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EXERCISE IN DIABETES MELLITUS

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Exercise along with diet and insulin is an accepted part of the present day treatment of diabetes.[1] Its ability to increase the blood sugar-lowering effect of insulin is well recognized.[2] Under certain conditions, however, exercise may cause a marked *increase* in the sugar content of the blood of a diabetic subject. This occurs particularly if the diabetic condition is severe and if several hours have elapsed since insulin and food were given. Such a finding is in keeping with the clinical observation of the preinsulin days that, whereas patients with mild diabetes profited by exercise, those with severe diabetes were often unable to tolerate it.[3]

In this connection the studies of Grote,[4] Bürger and Kramer [5] and Richardson [6] are of especial interest. Richardson found that the effect

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1. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 5, Philadelphia, Lea & Febiger, 1935, pp. 299-301.

2. Lawrence, R. D.: The Effect of Exercise on Insulin Action in Diabetes, Brit. M. J. **1**:648 (April 10) 1926. Gerl, A., and Hofmann, A.: Muskelarbeit und Insulinbedarf beim Diabetes, Klin. Wchnschr. **7**:59 (Jan. 8) 1928.

3. Allen, F. M.; Stillman, E., and Fitz, R.: Total Dietary Regulation in the Treatment of Diabetes, Monograph 11, Rockefeller Institute for Medical Research, 1919, p. 468. von Noorden, C. H., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, ed. 8, Berlin, Julius Springer, 1927, pp. 133-136. Lichtwitz, L.: Ueber den Einfluss der Muskelarbeit auf den Gehalt des Blutes an Zucker und Milchsäure, Berl. klin. Wchnschr. **51**:1018 (June 1) 1914. Külz, E., and Rumpf, T.: Klinische Erfahrungen über Diabetes mellitus, Jena, Gustav Fischer, 1899.

4. Grote, L. R.: Ueber die Beziehungen der Muskelarbeit zum Blutzucker, Halle, Carl Marhold, 1918.

(Footnotes continued on next page)

of exercise on the diabetic patient depended on the initial level of the blood sugar. In patients who had been given neither food nor insulin for sixteen hours exercise caused a decrease in the blood sugar content when the initial value was below 175 mg. per hundred cubic centimeters and an increase when the initial value was above 300 mg. per hundred cubic centimeters.

METHODS

Young diabetic patients in good physical condition were chosen for the tests. Except when otherwise stated, all the studies here reported were carried out in the early morning after an overnight fast of from twelve to fourteen hours. All injections of insulin were made subcutaneously.

Exercise of three types was employed: running at a definite rate, working on a rowing machine and stair climbing. Since we were not interested in closely comparing patient with patient and since the amount of work in each case had to be governed by the ability of the patient to perform it, no standardized amount of exercise was adopted. Every care was taken, however, to secure adequate control curves, and to ascertain under various conditions the effect of a given amount of work on each patient. Exercise was never carried to the point of undue fatigue.

Capillary blood obtained by puncture of the lobe of the ear or of a finger was used for the determinations of sugar. Samples were collected before each test was started and at frequent intervals throughout the test, which lasted usually for from one to two hours. Sugar was determined according to the micromethod of Folin.[7]

RESULTS

Case 1.—Mr. N. C., 27 years of age, with severe diabetes of six years' duration, was admitted to the New England Deaconess Hospital with extensive cellulitis of the face and neck. Improvement was slow because of persistent infection of the skin and subcutaneous tissues and recurrent superficial abscesses. Eleven months later, when the patient was up and about and was ready for discharge, exercise studies were carried out. With a diet of 211 Gm. of carbohydrate, 94 Gm. of protein and 100 Gm. of fat daily and with the use of from 56 to 60 units of insulin a day, the diabetic condition was under good control.

Chart 1 shows the effect of exercising on a rowing machine on the blood sugar levels of this patient. The solid black blocks represent periods of exercise, and their length is indicative of the duration of the activity. Between the periods of exercise the patient lay or sat quietly. Curves *A* and *B* are particularly to be contrasted. The former shows the striking rise in the blood sugar content which followed exercise without insulin (the patient had had no insulin since 2 units was given at midnight). Curve *B* shows the equally striking fall obtained when 8 units of insulin was given at 5:30 a.m., ninety-eight minutes before the exercise was begun. Curves *C* and *D* are control curves and represent the behavior of the

5. Bürger, M., and Kramer, H.: Ueber die durch Muskelarbeit hervorgerufene Steigerung der Insulinwirkung auf den Blutzuckergehalt beim normalen und gestörten Kohlehydratstoffwechsel und ihre praktische und theoretische Bedeutung, Klin. Wchnschr. **7**:745 (April 15) 1928.

6. Richardson, R.: Factors Determining the Effect of Exercise on Blood Sugar in the Diabetic, J. Clin. Investigation **13**:699 (July) 1934.

7. Folin, O., and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115 (July) 1929.

blood sugar level without and with insulin, respectively, with the subject at rest (lying in bed). In the case of Curve *D*, 8 units of insulin was given at 5:30 a. m., sixty-eight minutes before the first blood sugar value was recorded. In themselves curves *C* and *D* are interesting, for they demonstrate well the morning rise of the blood sugar level which may occur in a patient with severe diabetes and the effect on this of a relatively small dose of insulin.

It was thought desirable to determine the effect of another type of exercise. Accordingly, serial determinations of blood sugar were made before and after

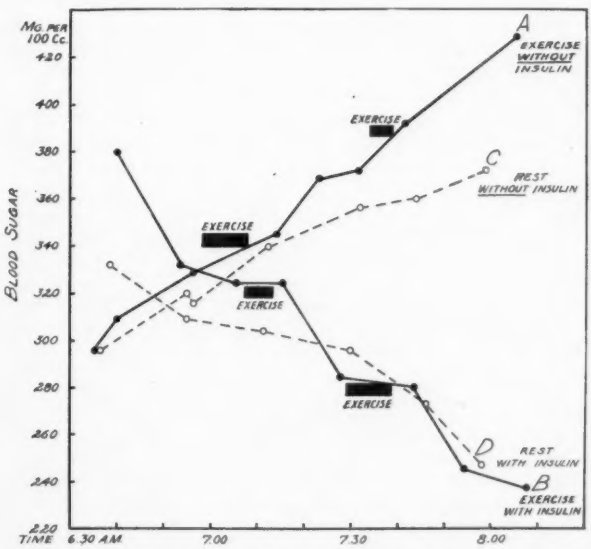

Chart 1 (case 1, Mr. N. C.).—Curve *A:* No insulin had been given since the midnight dose of 2 units, six and one-half hours prior to the exercise test on June 9. The first period consisted of rowing on a machine at a moderate rate, twenty-two strokes per minute, for ten minutes. The second period consisted of more active rowing, twenty-eight strokes per minute, for five minutes. Curve *B:* Eight units of insulin was given at 5:30 a. m. on June 14. The first period of exercise consisted of mild activity, twenty-one strokes per minute on a rowing machine, for five minutes. The second period consisted of moderate activity, twenty-seven or twenty-eight strokes per minute, for ten minutes. Curve *C:* No insulin had been given since the midnight dose of 2 units, six and one-half hours before the experimental period was begun on June 10, the patient resting during that period. Curve *D:* Eight units of insulin was given at 5:30 a. m. on June 13, the subject being at rest throughout the period noted. It will be seen from curve *A* of this and certain of the other charts that there was a slight rise in the blood sugar content before the exercise was begun. We attribute this to the fact that usually after one or two control samples of blood had been secured with the patient in bed, he was allowed to get up, dress partly and walk a short distance to the place where the studies were to be carried out. Before the exercise was actually begun an additional control sample was taken. This sample, probably because of the small amount of activity which had been permitted, at times had a slightly higher sugar content than the samples taken before the patient had stirred from bed.

this patient had walked or run for short periods. The studies were carried out with the patient in the fasting state. No food had been given since the evening meal of the previous day, and no insulin had been administered since the dose of 2 units at midnight. The rise in the blood sugar content was striking, as is evident from table 1.

Case 2.—G. D., a 13.8 year old boy, who had had diabetes since the age of 4.7 years, was in good physical condition at the time the exercise tests were made. With a diet containing carbohydrate, 170 Gm.; protein, 84 Gm., and fat, 86 Gm., and with the use of from 34 to 40 units of insulin a day, the diabetic condition was under fairly good control.

Chart 2 shows the effect of exercise on the blood sugar content. Curve *A* demonstrates the rise obtained (from 300 to 396 mg. per hundred cubic centimeters in seventy-five minutes) when the patient had had no insulin since the dose of 2 units at 10 p. m. the preceding day. Unfortunately the control curve *B* starts at a considerably higher level, but in its extent it shows relatively little tendency to rise.

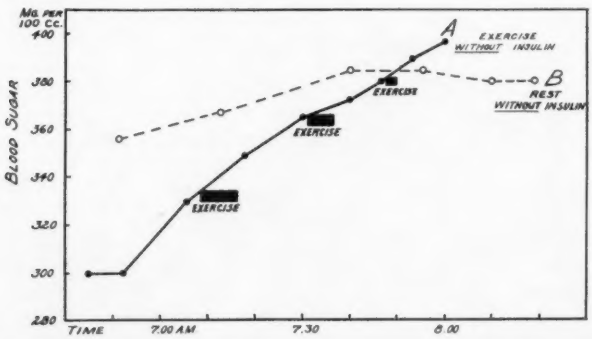

Chart 2 (case 2, G. D.).—Curve *A:* No insulin had been given since a dose of 2 units at 10 p. m., eight and three-fourth hours before the exercise was begun on March 29. The first two periods of exercise consisted of rowing on a machine at a moderate rate for eight and six minutes, respectively. The third period consisted of running at low speed (a "dog trot") for two minutes. Curve *B:* No insulin had been given since a dose of 2 units at 10 p. m., eight and three-fourths hours before the experimental period on March 28, the subject resting during that period.

Table 1.—*Data on the Effect of Exercise on the Blood Sugar Content**

Time, a. m.	Blood Sugar, Mg. per 100 Cc.	Comments
6:53	480	Patient in bed
7:06	488	Patient in bed
7:15-7:22	...	Walking at approximately 4 miles per hour
7:27	496	
7:36	524	
7:40-7:45	...	Running at moderate rate with short final spurt of 30 seconds
7:49	532	
8:10	564	
8:19	564	

* Mr. N. C., case 1, had received no insulin for seven hours prior to exercise on June 24.

The results of other control studies which were carried out with this patient may be summarized as follows:

Exercise with insulin on March 30: The patient was given 5 units of insulin subcutaneously at 5:30 a. m. The last previous dose of insulin was 4 units at 10 p. m. the preceding day. The blood sugar value at 6:50 a. m. was 192 mg. per hundred cubic centimeters. After two separated periods of exercise on the rowing machine (for six and five minutes, respectively) and running at a brisk "dog trot" for three minutes, the blood sugar value was 150 mg. at 7:24 a. m., 128 mg. at 7:46 a. m. and 114 mg. at 8:02 a. m.

Rest with insulin on March 31: The patient was given 5 units of insulin subcutaneously at 5:30 a. m. The last previous dose of insulin was 4 units at 10 p. m. the preceding day. The blood sugar value at 6:47 a. m. was 246 mg. per hundred cubic centimeters. The patient rested in bed throughout the study period while

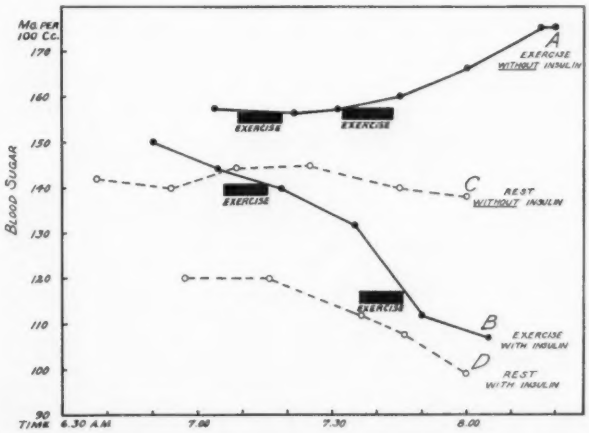

Chart 3 (case 3, Mr. C. H.).—Curve *A:* On May 15 no insulin had been received for over twelve hours before the experimental period. The two periods of exercise consisted of rowing a machine at a moderate speed for ten and eleven minutes, respectively. Curve *B:* On May 11 the conditions were the same as for curve *B* except that at 6:53 a. m. 8 units of insulin was given. Curve *C:* On May 9 no insulin had been given for over twelve hours, and the patient was at rest in bed during the experimental period. Curve *D:* On May 12 the conditions were the same as for curve *C* except that at 6:58 a. m. 8 units of insulin was given.

determinations of blood sugar were made at intervals. The blood sugar value was 172 mg. at 7:25 a. m., 144 mg. at 7:52 a. m. and 137 mg. at 8:01 a. m.

Case 3.—Mr. C. H., 30 years of age, had had diabetes for four months. He was in good general health when the exercise tests were carried out. With a diet containing carbohydrate, 173 Gm.; protein, 80 Gm., and fat, 116 Gm., and with the use of from 22 to 30 units of insulin a day the diabetic condition was under good control.

Chart 3 shows again in curve *A* the rise in the blood sugar content which follows exercise when no insulin has been given previously. The exercise in this

instance consisted of the use of the rowing machine at a moderate rate for two periods of ten and eleven minutes, respectively. The last dose of insulin had been given at about 6 p. m. the preceding day.

Curve *B* shows the characteristic fall produced by exercise (on the rowing machine) when insulin has been given shortly before. In this instance the patient received 8 units of insulin at 6:53 a. m. Curve *C* is a control curve. Without insulin or food the blood sugar content with the patient at rest remained practically constant. This contrasts with the corresponding curve in chart 1, the difference undoubtedly being due to the fact that the diabetic condition in case 1 was much more severe than that in case 3. Curve *D* shows the fall in the blood sugar content which took place with the patient at rest when 8 units of insulin was given at 6:58 a. m.

In addition to these tests, the effect of running at moderate speed (over a mile in ten minutes) was determined. In table 2 are listed the findings. The subject was in the fasting state and had had no insulin for thirteen hours. That a definite rise in the blood sugar level was obtained is shown in table 2.

TABLE 2.—*Data on the Effect of Exercise on the Blood Sugar Content**

Time, a. m.	Blood Sugar, Mg. per 100 Cc.	Comments
7:07	169	Resting in bed
7:10	174	Resting in bed
7:15-7:25	...	Running at rate of 6 or 7 miles per hour
7:28	185	
7:28-7:52	...	Mild activity about room
7:52	194	
8:10	213	Resting in bed
8:23	216	Resting in bed

* Mr. C. H., case 3, had received no insulin for thirteen hours prior to the test on May 18.

Because of the results obtained in the early morning, the patient was naturally interested to know how exercise in the late afternoon would affect the blood sugar content, particularly since no insulin was taken before the noon meal. Accordingly, on two successive days he was allowed to take two short periods of exercise (rapid walking or running) about three hours after lunch. The results are shown in table 3.

On each occasion the exercise caused a marked lowering of the blood sugar content. This definite effect was surprising in view of the fact that the patient had received no insulin for eight hours.

In going over Richardson's [6] results we note that he obtained similar results in two cases. By omitting the morning insulin entirely and repeating the test he obtained the same result and so assumed that the "intake of food provided a condition which, with exercise, resulted in reduction of blood sugar." It is possible that the effect of food has been to increase the amount of effective endogenous insulin. This conclusion is strengthened by the findings of Bürger and Kramer [5] and of

Strandell,[8] although Hetzel and Long[9] from not entirely comparable experiments reported that in the diabetic patient the reduction by exercise of postcibal hyperglycemia occurred only when insulin had been recently administered.

CASE 4.—R. A., a 13.1 year old boy, had had diabetes for six and seven-tenths years. With a diet of carbohydrate, 281 Gm.; protein, 99 Gm., and fat, 55 Gm., allowing 2,015 calories per day and with 56 units of insulin a day, the diabetic condition was under good control. The physical condition was fairly good, and examination showed no abnormalities except enlargement of the liver.

Chart 4 shows strikingly the elevation of the blood sugar content caused by two periods of stair climbing of five minutes each with the patient in the fasting

TABLE 3.—*Data on the Effect of Exercise in the Late Afternoon on the Blood Sugar Content**

Time, p. m.	Blood Sugar, Mg. per 100 Cc.	Comments
May 31, 3:39	224	
3:51	225	
4:05	220	
4:10-4:20	...	Walking briskly ¾ mile
4:28	193	
4:30-4:38	...	Running ¾ mile
4:42	187	
5:20	164	
5:30	163	
June 1, 4:29	188	
4:32	190	
4:45	182	
4:56	175	
4:57-5:07	...	Walking briskly ¾ mile
5:10	164	
5:11-5:16	...	Running ¾ mile
5:20	160	
5:35	144	
5:54	132	
6:15	124	
6:21	112	

* Mr. C. H., case 3, on May 31 had a last dose of 16 units of insulin at 7:20 a. m. He took a normal amount of exercise during the day and had lunch at 12:45 p. m. On June 1 he had a last dose of 14 units of insulin at 7:40 a. m. He took a moderate amount of activity during the day and had lunch at 12:45 p. m.

state. He had had no insulin since 10 p. m. (4 units) the previous evening. In five minutes he was able to go twice up and down ninety-eight steps, each 18.5 cm. high. He was only mildly fatigued at the end of the period of exercise. The body weight was 77¼ pounds (35.3 Kg.).

Curve *B* is a control curve showing the behavior of the blood sugar content with the patient at rest throughout the experiment (no insulin since 4 units at 10 p. m. the previous evening).

8. Strandell, B.: On the Influence of Exercise on the Blood Sugar, Especially in Connection with Glucose Ingestion, Acta med. Scandinav. (supp.) **55**:1, 1934. In this monograph and in the paper of F. W. Lapp and C. L. Torriani (Blutzuckertagesablauf beim arbeitenden Diabetiker, Ztschr. f. klin. Med. **117**:425, 1931) there are good bibliographies.

9. Hetzel, K. S., and Long, C. N. H.: The Metabolism of the Diabetic Individual During and After Muscular Exercise, Proc. Roy. Soc., London, s.B **99**: 279 (March 1) 1926.

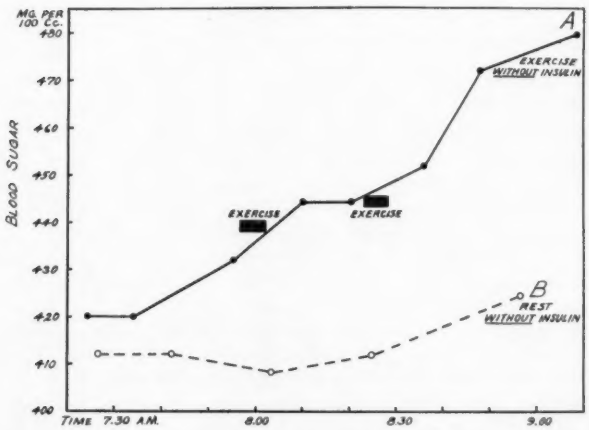

Chart 4 (case 4, R. A.).—Curve *A:* No insulin had been given since a dose of 4 units at 10 p. m., more than nine hours before the experimental period was begun on March 21. The two periods of exercise consisted of stair climbing for five minutes each. Curve *B:* No insulin had been given since a dose of 4 units at 10 p. m., over nine hours before the experimental period was begun on March 22, the patient being at rest during that time.

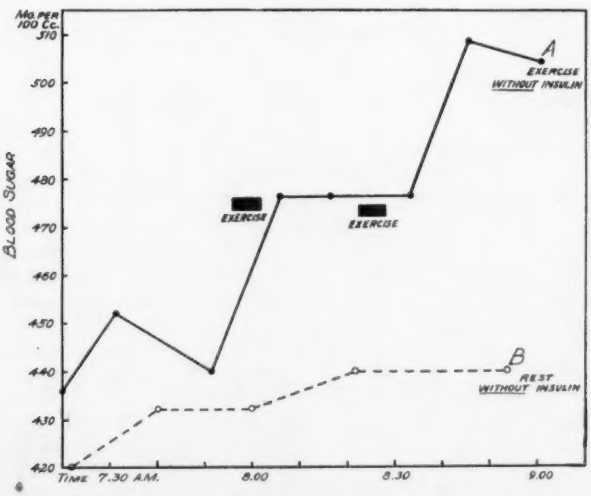

Chart 5 (case 5, T. R.).—Curve *A:* No insulin had been given since a dose of 6 units at 10 p. m., nine hours before the experimental period was begun on March 21. The exercise consisted of stair climbing for five minutes. Curve *B:* No insulin had been given since a dose of 6 units at 10 p. m., nine hours before the beginning of the experimental period, the patient being at rest during that time.

CASE 5.—T. R., a 13.8 year old boy, had had severe diabetes for nine and eight-tenths years. The diabetic condition was under good control with a diet of carbohydrate from 199 to 221 Gm.; protein, 123 Gm., and fat, 106 Gm., and with 68 units of insulin a day. This patient was a diabetic pseudodwarf and, like the patient just discussed, had an enlarged liver, presumably filled with fat. The body weight was 60 pounds (27.3 Kg.).

This patient did exactly the same amount of stair climbing as the previous patient (case 4). The exercise tired him a trifle more, but the fatigue was slight and short lived. The results are shown in chart 5. In this case also exercise without insulin produced an unmistakable rise in the blood sugar value.

COMMENT

The foregoing results demonstrate that in the fasting patient with severe or moderately severe diabetes who has received no injection of insulin for several hours the immediate result of exercise may be that of raising the blood sugar level. This contrasts with the effect seen in the normal nondiabetic subject, in whom moderate exercise of short duration causes little if any change in the blood sugar content.[10] It is true that in normal persons more strenuous exercise, although it is of short duration, may cause a significant transient rise in the blood sugar content (*primäre Arbeitshyperglycämie*[11]), but this is not nearly as marked or as constant as in the diabetic subject. Moreover, when the exercise is strenuous and prolonged, a decided decrease producing hypoglycemia may result.[12]

Exercise apparently stimulates the breakdown of glycogen in the liver, with a resulting outpouring of sugar into the blood stream. It is probable that this glycogenolysis is attributable in part to an increased secretion of epinephrine caused by the exercise. Thus, Hartman,[13] using the denervated pupil as an index, has shown that in normal cats there occurs an increase in the output of epinephrine during exercise on a treadmill. This is further borne out by the work of Cannon, Linton and Linton[14] and (at least for severe work) by that of Dill,

10. Trimble, H. C., and Maddock, S. J.: The Fluctuations of the Capillary Blood Sugar in Normal Young Men During a Twenty-Four Hour Period (Including a Discussion of the Effect of Sleep and of Mild Exercise), J. Biol. Chem. **81**:595 (March) 1929.

11. Solandt, O. M., and Ferguson, G. C.: The Effect of Strenuous Exercise of Short Duration upon the Sugar Content of the Blood, Tr. Roy. Soc. Canada, sect. 5, 1932, p. 173. Bürger and Kramer.[5]

12. Levine, S. A.; Gordon, B., and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, J. A. M. A. **82**:1778 (May 31) 1924. Best, C. H., and Partridge, R. C.: Observations on Olympic Athletes, Proc. Roy. Soc., London, s.B **105**:323 (Sept. 2) 1929.

13. Hartman, F. A.: The Relation of the Adrenals to Muscular Activity, Endocrinology **6**:511 (July) 1922.

14. Cannon, W. B.; Linton, J. R., and Linton, R. R.: Conditions of Activity in Endocrine Glands: XIV. The Effects of Muscle Metabolites on Adrenal Secretion, Am. J. Physiol. **71**:153 (Dec.) 1924.

Edwards and Mead.[15] One must point out, however, that Katz [16] was unable to demonstrate in human subjects an increase in the epinephrine content of the blood during exercise.

In the normal subject this flow of sugar from the liver is probably not as great as it is in the diabetic patient, since the stores of glycogen in the liver of the diabetic patient are comparatively less stable; furthermore, hyperglycemia is less severe because the sugar released is quickly used by the muscles. In the completely diabetic organism, however, as has been shown by Yater and his co-workers,[17] contracting muscle is unable to utilize the dextrose molecule to obtain extra energy (although the dextrose requirement of the *resting* skeletal muscle is the same in the diabetic as in the nondiabetic state). These investigators regard it as a function of insulin to elaborate dextrose utilization by the muscle. It seems reasonable to suppose that in the diabetic patient the unutilized sugar accumulates in the blood stream, producing the hyperglycemia noted in the studies reported in this paper.

Richardson [6] found that although the diabetic subject with a normal blood sugar value during fasting responded to exercise in an essentially normal fashion, the patient with slightly more severe diabetes (with a fasting blood sugar value of approximately 175 mg. per hundred cubic centimeters) showed after exercise an even greater drop than a normal subject. He explained such results on the assumption that although the patient is able to withdraw sugar from the blood in a fashion approaching the normal, the glycogen stores of the body are not adequate to afford protection from hypoglycemia. In our subjects no response of this type was observed. Even in case 3, in which the blood sugar value during fasting varied from 120 to 188 mg. per hundred cubic centimeters, definite increases in the blood sugar content were obtained after moderate exercise.

It is evident that such studies bear a direct relationship to the treatment of diabetic patients. In the first place, they point out definitely the value of adequate control of the diabetic condition. The diabetic patient of today leads an essentially normal life, with an average amount of activity. If the diabetic condition is imperfectly controlled and if the body has been supplied with an inadequate amount of insulin, then exercise instead of conferring benefit may actually increase the hyperglycemia and glycosuria.

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15. Dill, D. B.; Edwards, H. T., and Mead, S.: Bood Sugar Regulation in Exercise, Am. J. Physiol. **111**:21 (Feb.) 1935.

16. Katz, G.: Ueber den Adrenalingehalt des peripheren menschlichen Blutes bei Muskelarbeit, Ztschr. f. klin. Med. **123**:154, 1933.

17. Yater, W. M.; Markowitz, J.; Cahoon, R. F., and Burrows, W. H.: Consumption of Blood Sugar by Muscle in the Nondiabetic and in the Diabetic State, Arch. Int. Med. **51**:800 (May) 1933.

Our results suggest another point with regard to treatment. For exercise to exert its maximum benefit sufficient insulin must be available in the body at the time of exercise. Practically speaking, after he arises in the morning the logical sequence for the diabetic patient is insulin, exercise and breakfast rather than exercise, insulin and breakfast. The exercise should be mild enough so that undue fatigue is not produced. The further advantage of two, three or more additional periods of exercise during the day is obvious.

In their studies on the effect of muscular exercise in two carefully controlled cases of uncomplicated diabetes, Soskin, Strouse and their colleagues [18] were unable to show "significant improvement in the diabetic tolerance or a decrease in the insulin requirements." Their results, although obtained for only two patients, were definite and unmistakable. One must agree, then, that exercise does not cause any fundamental change in the severity of the diabetic condition. (The improvement in physical fitness and muscular development produced by exercise will be conceded by all.) One knows, however, that by taking advantage of temporary decreases in the blood sugar content caused by insulin *plus exercise,* one may materially increase the amount of food given without any increase in the dosage of insulin. This was not brought out in the studies of Soskin and his associates, because their patients were kept on a constant diet and dosage of insulin. If, however, one gives additional food at those times of the day—commonly in the late forenoon, in the late afternoon and at bedtime—when by the combined effect of insulin and exercise the blood sugar value is lowest, one can easily demonstrate that on days of muscular activity much more food can be tolerated with the same or even a smaller amount of insulin than on days of relative inactivity. Priscilla White [19] has brought out this point strikingly in her studies of diabetic children at summer camps. One is impressed by the fact that under carefully controlled conditions, which include the accurate weighing of food, the frequent estimation of the blood sugar value and the daily determination of the quantity of sugar excreted in the urine, these young patients with severe diabetes tolerate more food and are in better health than during the winter, when for a large part of the day they are at school and inactive. To be sure, the exercise makes the diabetic condition no milder, and there is no significant lasting gain in tolerance which can be attributed to the exercise per se, but the end-result for the period of activity is the same, namely, the actual utilization of more food with the same or a lessened need for insulin.

18. Soskin, S.; Strouse, S.; Molander, C. O.; Vidgoff, B., and Henner, R. I.: Value of Muscular Exercise in the Treatment of Diabetes Mellitus, J. A. M. A. **103**:1767 (Dec. 8) 1934.

19. White, Priscilla: Personal communication to the authors.

SUMMARY

Exercise of short duration carried to the point of only mild fatigue invariably caused a definite and often a marked increase in the concentration of sugar in the blood of young patients with severe or moderately severe diabetes who had not received food or insulin for several hours.

The practical bearing of this finding on the use of exercise in the treatment of diabetes is discussed.

NOTE.—Since the completion of the foregoing studies and the preparation of the manuscript, slowly-acting protamine insulinate has been introduced (Hagedorn, H. C.; Norman Jensen, B.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106:** 177 [Jan. 18] 1936). It is evident that in this preparation, the effect of which lasts for from twelve to thirty hours, one has a means of keeping the level of the blood sugar of the patient with severe diabetes more nearly normal for a greater part of the twenty-four hours than is possible with regular insulin as ordinarily administered. A patient receiving an adequate amount of protamine insulinate should always have some insulin available in the body. Hence, exercise should exert a lowering effect on the blood sugar level in such a subject at practically all times.

CHOLESTEROL CONTENT OF BLOOD IN DIABETIC PATIENTS FED DIETS RICH IN FAT

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During recent years there has been increasing interest in the blood lipids in patients with diabetes mellitus, chiefly because of the uncertain relationship between dietary fat, hypercholesteremia and the frequent development of atherosclerosis in diabetic subjects. It has been repeatedly demonstrated that atherosclerosis can be produced in rabbits by feeding large amounts of cholesterol. It is also well known that many diabetic patients have hypercholesteremia, that arteriosclerosis develops at a relatively early age in many diabetic patients and that this complication accounts for most of the incapacitation and fatality from this disease. The cause of a high cholesterol content of the blood and of vascular disease in diabetic patients has naturally been the subject of much investigation.

Before the advent of insulin it was necessary for all patients with diabetes except those with mild involvement to live on a high fat-low carbohydrate diet. Since 1922, with the use of insulin, a sharp restriction of carbohydrate has no longer been imperative. As a result, diets with less fat and more carbohydrate than were common in preinsulin days are being used in most clinics. During the change in trend from diets with a higher to those with a lower fat content there has been reported a general lowering of the cholesterol content of the blood. Joslin [1] has reported that the average cholesterol value for his diabetic patients fell from 385 mg. per hundred cubic centimeters of blood in 1917 to 208 mg. in 1934. He stated that this lower average value for cholesterol can be explained on the basis that the diets used in his clinic in recent years contained less fat and more carbohydrate than formerly. In fact, the opinion is prevalent that diabetic diets rich in fat cause hypercholesteremia and subsequently arteriosclerosis.

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1. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 5, Philadelphia, Lea & Febiger, 1935.

Since the diabetic clinic of the University Hospital is one of the few which prescribe diets rich in fat, the cholesterol content was determined in a series of diabetic patients who had been on these diets, in order to determine whether there was any consistent relationship between the ingestion of fat and the level of cholesterol in the blood.

METHOD

Only patients whose diabetes had been controlled for two months or longer while they had been eating the same diet were studied. The precaution that the diabetes be controlled was felt to be highly important, in order that the effects of hyperglycemia, glycosuria and acidosis on the cholesterol level of the blood would be eliminated. Female patients were studied in the intermenstrual period in order to avoid changes in the cholesterol content accompanying the menses.[2]

Specimens of blood taken during fasting were analyzed for cholesterol by the Windaus[3] gravimetric digitonide method during the early portion of the study; later the Okey[4] modification of this method, employing oxidation of the digitone, was used.[5] These two procedures gave similar results in our laboratory. The digitonin method of analysis was selected because of its greater accuracy as compared with the more commonly employed colorimetric method. Mühlbock and Kaufmann[6] have stated that the inaccuracies of the colorimetric method may vary from minus 18 to plus 76 per cent.

The essential information obtained in this study appears in the accompanying table, in which the data for twenty-one patients are listed according to the number of the dietary calories supplied by fat.

The Normal Level of Cholesterol in the Blood.—It is difficult to know the true normal level of the cholesterol in the blood during fasting. Values given in the literature vary widely, owing chiefly to differences in the analytic methods employed. Digitonin methods for the determination of the cholesterol content ordinarily give values somewhat lower than methods based on the Liebermann-Burchard color reaction, because

2. Okey, R., and Boyden, R. E.: Studies of Metabolism of Women: Variations in Lipid Content of Blood in Relation to Menstrual Cycle, J. Biol. Chem. **72**:261 (March) 1927.

3. Windaus, S.: Ueber die quantitative Bestimmung des Cholesterins und der Cholesterinester in einigen normalen und pathologischen Nieren, Ztschr. f. physiol. Chem. **65**:110, 1910.

4. Okey, R.: A Micromethod for the Estimation of Cholesterol by Oxidation of the Digitonide, J. Biol. Chem. **88**:367 (Aug.) 1930.

5. In order to insure the complete extraction of lipids from the blood in each case the residue from the usual alcohol-ether extraction was ground in a mortar with fresh alcohol and ether; the mixture was then transferred to a beaker, heated to boiling, allowed to cool, filtered and washed twice with fresh alcohol and ether. This filtrate was then combined with the first extraction filtrate, and the analyses were carried out.

6. Mühlbock, O., and Kaufmann, C.: Die gravimetrische Cholesterinbestimmung im Blut und Serum, Biochem. Ztschr. **233**:222, 1931.

certain products of decomposition of sterols give the color reaction with greater intensity than the sterol itself.[7] In a comparative study recently made by Gibbs, Buckner and Bloor[8] it was found that the colorimetric method gave results about 30 per cent higher than the Okey digitonin method. These investigators found the range of the cholesterol value in normal persons to be from 183 to 307 mg. per hundred cubic

Data for Twenty-One Diabetic Patients

Patient	Sex	Age, Years	Other Diagnoses	Diet: Protein, Gm.	Diet: Fat, Gm.	Diet: Carbohydrate, Gm.	Calories	Calories of Diet Derived from Fat, %	Calories of Metabolic Mixture* Derived from Fat, %	Length of Time Diabetes Was Controlled on This Diet	Daily Dose of Insulin, Units	Cholesterol Content of Blood, Mg. per 100 Cc.
F. D. J.	M	36	None	58	274	63	2,947	84	84	8 yr.	32	176
N. K.	M	40	Chronic sinusitis; psychoneurosis	55	250	60	2,700	83	83	2 mo.	46	200
M. T.	F	60	None	55	220	65	2,460	81	81	5 yr.	30	126
B. W.	F	19	None	55	220	65	2,460	81	81	3 yr.	0	175
W. M.	F	15	None	55	220	95	2,500	80	80	5 mo.	36	131
H. B. L.	M	20	Undernutrition	70	320	120	3,600	80	76	3 mo.	0	132
R. N.	M	17	None	70	260	80	3,000	80	80	8 mo.	55	223
M. T. T.	F	63	None	55	220	70	2,500	80	80	15 mo.	36	202
J. W.	M	18	None	70	220	80	3,000	80	75	2 mo.	0	167
Average	..	..	.....	..	...	..	.....	81	..	.....	..	170
R. H.	F	59	None	55	155	45	1,800	78	78	4 yr.	0	180
F. F.	M	44	None	55	175	45	2,000	78	84	2 mo.	0	220
G. L.	M	49	Arteriosclerosis; chronic nephritis; neuroretinitis; slight obesity	55	200	115	2,500	73	73	3 yr.	0	186
R. D.	M	16	None	55	200	95	2,460	73	73	3 yr.	60	152
G. B.	F	15	None	50	160	90	2,000	72	72	20 mo.	64	202
S. F.	M	18	None	55	220	150	2,800	71	71	20 mo.	30	210
M. E. C.	F	58	Hypertension; obesity	50	90	44	1,200	68	82	2 mo.	0	223
M. Mc.	F	14	None	69	150	95	2,000	67	67	5 mo.	45	173
L. R.	F	38	None	58	131	123	1,920	61	61	18 mo.	36	203
M. N.	F	45	Hypertension	55	150	150	2,200	60	60	5 mo.	0	165
R. N. S.	F	44	Obesity; mild nephritis	50	65	110	1,300	49	74	2 mo.	25	159
E. S.	F	58	Obesity; arteriosclerosis; incipient cataracts	52	50	90	1,000	43	74	2 mo.	0	150
Average	..	..	.....	..	...	..	.....	66	..	.....	..	185
Average for all cases												179

* Estimated as described in the text.

centimeters of plasma by the colorimetric method. In Joslin's clinic, where the colorimetric method is used, the normal range is considered to be from 100 to 230 mg. per hundred cubic centimeters.[1] Different

7. Lifschütz, I.: Die Abbauprodukte des Cholesterins in den tierischen Organen, Ztschr. f. physiol. Chem. **117**:201 (Dec.) 1921.

8. Gibbs, C. B. F.; Buckner, E., and Bloor, W. R.: The Cholesterol to Cholesterol Ester Ratio in the Plasma of Diabetics with Advanced Arteriosclerosis, New England J. Med. **209**:384 (Aug. 24) 1933.

modifications of the digitonin precipitation method may give slightly different results. With a modified gravimetric digitonin method Man and Peters [9] found that the cholesterol values during fasting for ten normal persons ranged between 162 and 256 mg. With an oxidative digitonin method Boyd [10] recently found that the cholesterol values for normal young women range between 112 and 195 mg. per hundred cubic centimeters of plasma, the mean being 162 mg. In this laboratory analysis of the blood of twenty-one normal persons from 18 to 62 years of age, equally divided as to sex, showed cholesterol values during fasting between 130 and 186 mg. per hundred cubic centimeters of blood, the average being 156 mg.

In view of the foregoing discussion, it is readily seen that the interpretation of *small* differences in the cholesterol values of the blood is impossible and that a comparison of the values from different clinics is difficult because of the different methods used.

The Relationship Between Dietary Fat and the Cholesterol Content.—The level of cholesterol in all the patients studied ranged from 126 to 223 mg. per hundred cubic centimeters of blood, the average being 176 mg. It is seen that there is no correlation between the amount of fat in the diet and the cholesterol level of the blood. The following cases exemplify this lack of correlation. M. T., whose dietary fat furnished 81 per cent of the ingested calories, had a cholesterol value of only 126 mg. per hundred cubic centimeters of blood, the lowest value observed, whereas M. E. C., whose dietary fat contributed only 68 per cent of the calorific value of the diet, had a cholesterol value of 223 mg. per hundred cubic centimeters of blood, the highest value found (equal to that of R. N.).

Lack of any direct relationship between the amount of dietary fat and the level of cholesterol in the blood is further shown when average values are considered. Nine patients were on diets in which 80 per cent or more of the calorific value was supplied in the form of fat. The cholesterol values in this group ranged from 126 to 223 mg., the average value being 170 mg. This is especially significant when it is noted that the twelve patients whose dietary fat made up only from 43 to 78 per cent of the total caloric content had cholesterol values ranging from 150 to 223 mg., the average being 185 mg. The average cholesterol value was less in the diabetic patients who ingested the most fat.

9. Man, E. B., and Peters, J. P.: Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method, with a Note on the Estimation of Lipoid Phosphorus, J. Biol. Chem. **101**:685 (Aug.) 1933.

10. Boyd, E. M.: A Differential Lipid Analysis of Blood Plasma in Normal Young Women by Micro-Oxidative Methods, J. Biol. Chem. **101**:323 (June) 1933.

Some of the patients studied were overweight and were accordingly on reduction diets. The metabolic mixture of each of these patients was calculated from the change in weight, assuming the caloric deficit to be made up entirely from body fat. The average cholesterol value of the blood in all whose metabolic mixture showed 80 per cent or more of the calories to be derived from fat (nine patients) was 186 mg. per hundred cubic centimeters. The remainder, those whose metabolic mixture showed a range of from only 60 to 78 per cent of fat, had an average cholesterol value of 173 mg. per hundred cubic centimeters. These average cholesterol values for the two groups differ by only 13 mg. and lie within the range of the values for the control group.

One patient (F. D. J.), a physician, had been on a diet of 58 Gm. of protein, 274 Gm. of fat and 63 Gm. of carbohydrate for eight years. This diet had a fatty acid-dextrose ratio of 2.4 (as customarily calculated), and 84 per cent of the 2,947 calories was derived from fat. Certainly if ingestion of a diet rich in fat causes hypercholesteremia, one would expect it to develop in this case. Actually, however, the cholesterol content was only 176 mg. per hundred cubic centimeters of blood, a normal value.

There has been considerable animal experimentation and clinical study concerning the possible relationship between dietary fat and the level of lipids in the blood. The results of such investigations are conflicting. Allen,[11] for instance, observed the effect of diet in dogs and described his results as follows:

> Repeated and determined attempts were made to produce lipemia on the assumption that it might be the result of prolonged excess of fat or a preponderance of fat over carbohydrate or protein in the diet. One-sided fat diets were thus pushed to the point of producing peculiar fatal disturbances, to be described in detail later, but no significant grade of lipemia resulted in normal dogs, partially depancreatized non-diabetic dogs, or diabetic dogs free from glycosuria.

More recently Bloor[12] has found that "in both dogs and rabbits increasing the proportion of fat in the diet results in increased plasma phospholipoid and cholesterol, but in the dogs the increase is inconsiderable, while in the rabbits it is great."

Rabinowitch,[13] who has recorded the cholesterol values for a large number of diabetic patients under a great many different conditions,

11. Allen, F. M.: Experimental Studies in Diabetes: The Production of Diabetic Lipemia in Animals, and Observations on Some Possible Etiologic Factors, J. Metabolic Research **2**:219 (Aug.) 1922.

12. Bloor, W. R.: Diet and the Blood Lipids, J. Biol. Chem. **95**:633 (March) 1932.

13. Rabinowitch, I. M.: Arteriosclerosis in Diabetes: I. Relationship Between Plasma Cholesterol and Arteriosclerosis; II. Effects of High Carbohydrate-Low Calorie Diet, Ann. Int. Med. **8**:1436 (May) 1935.

has said that he is convinced that the level of cholesterol in the blood is directly related to the fat of the diet. He stated: "One of the most constant characteristics of the high carbohydrate-low caloric diet is an immediate and sustained decrease of plasma cholesterol." He pointed out that a number of factors contribute to hypercholesteremia, and of those other than the fat of the diet the lack of control of the disease is the most important.

In contrast, Boyd [14] found in his diabetic children that diets rich in fat (from 64 to 84 per cent of the energy value derived from fat) did not cause hypercholesteremia. Recently, Man and Peters [15] reported that in a study of seventy-nine diabetic patients on diets rich in fat the cholesterol value of the blood was normal in forty-two, above normal in twenty-eight and below normal in nine. Their diets contained, as a rule, from 125 to 175 Gm. of fat. In an attempt to correlate the cholesteremia with dietary fat, they found it "impossible to relate either cholesterol or lipemia to fat intake." Their data are confusing in one respect, however; the blood sugar level was considerably above normal in many of the patients, indicating that the diabetic condition was not controlled in all cases. It is mentioned that no patient was dehydrated or acidotic.

Joslin [1] has repeatedly warned against the use of a diabetic diet rich in fat, inferring that such a diet would produce hypercholesteremia. Yet he [16] reports the personal observation of a patient who had lived for sixteen years on a diet low in carbohydrate, whose diabetes was controlled and who showed a cholesterol value which, much to his astonishment, was normal.

Relationship Between Hypercholesteremia and Arteriosclerosis.—A number of years ago one of us (L. H. N.[17]) reported the production of atherosclerosis in rabbits fed cholesterol. Some of the results of that study are of sufficient interest to be recalled in connection with this discussion. In a group of animals that received 113 mg. of cholesterol daily the mean cholesterol value of the blood was normal (80 mg. per hundred cubic centimeters). Four animals in this group had cholesterol values just above the highest value for a control animal, but in none of these was there evidence of atherosclerosis. The only animal of this group with an atherosclerotic aorta had a normal cholesterol

14. Boyd, G. L.: Blood Cholesterol in Diabetic Children, Am. J. Dis. Child. **38**:490 (Sept.) 1929.

15. Man, E. B., and Peters, J. P.: Serum Lipids in Diabetes, J. Clin. Investigation **14**:579 (Sept.) 1935.

16. Joslin, E. P.: Fat and the Diabetic, New England J. Med. **209**:519 (Sept. 14) 1933.

17. Clarkson, S., and Newburgh, L. H.: The Relation Between Atherosclerosis and Ingested Cholesterol in the Rabbit, J. Exper. Med. **43**:595 (May) 1926.

value. Of the group fed 250 mg. of cholesterol daily for more than two hundred days, an atherosclerotic aorta was found in those with a normal as well as in those with a high blood cholesterol value, although the animal that exhibited the most extreme hypercholesteremia had a normal aorta. Seven rabbits were fed 500 mg. of cholesterol daily. In all of these animals well marked hypercholesteremia developed, and five became atherosclerotic. The statement was therefore made: "It may be that there exists a causal relationship between the cholesterol in the blood and the state of the vessel; but we have not sufficient data dealing with the question to be in a position to give a final answer."

Such experiments, in which rabbits were fed cholesterol with the production of hypercholesteremia and later atherosclerosis, suggested that hypercholesteremia is a factor in causing arteriosclerosis in diabetic patients. Yet there is no clearcut evidence that this is true. Gibbs, Buckner and Bloor [8] have recently found slightly elevated cholesterol values in adult diabetic patients with arteriosclerosis. However, it is not mentioned whether the diabetes was controlled in these patients. It is noteworthy also that their patients with severe arteriosclerotic gangrene, necessitating amputation in many cases, were on diets with only 55 per cent of fat.

Joslin [16] stated that arteriosclerosis was fifteen times as frequent in his diabetic children who showed hypercholesteremia as in the group who had normal cholesterol values. In adult diabetic patients with arteriosclerosis studied in Joslin's clinic high cholesterol values were not found. In fact, in one study [18] it was observed that the cholesterol value was lowest in those patients who showed the most marked arteriosclerosis. In a recent study Man and Peters [15] found that severe arteriosclerosis with or without hypertension was evident in patients with cholesterol values that were normal, below normal and above normal, and they were unable to find any relationship between the level of the cholesterol and the degree of arteriosclerosis.

In this connection it is of interest to note that of the twenty-one patients who were the subject of this study only eight showed cholesterol values higher than our normal range—and these were only slightly higher. The highest value observed was 223 mg. per hundred cubic centimeters. There appeared to be no relation to the age of the patient; the ages were scattered between 15 and 63 years. There were four males and four females. It was previously pointed out that the cholesterol values could not be correlated with the amount of fat in the diet. What is the significance of the cholesterol values that were slightly higher than those in the normal subjects? Are cholesterol values of

18. Hunt, H. M.: Cholesterol in Blood of Diabetics Treated at the New England Deaconess Hospital, New England J. Med. **201**:659 (Oct. 3) 1929.

this level in any way injurious to the patient? We are unable to answer these questions with certainty. It should be noted, however, that in none of the patients whose cholesterol value was slightly higher than normal was evidence of arteriosclerosis revealed by careful physical examination. The two persons who had arteriosclerosis had cholesterol values of 150 and 186 mg. per hundred cubic centimeters, respectively.

The Effect of Controlling the Diabetes on the Level of the Blood Lipids.—The confusion in the literature regarding the relationship of ingestion of fat, marked hypercholesteremia and arteriosclerosis exists, in our opinion, chiefly because most investigators do not discriminate between diabetic patients whose disease is controlled and those in whom hyperglycemia, glycosuria and ketonuria exist. The factor of primary importance in the prevention of marked hypercholesteremia and hyperlipoidemia is *control of the diabetes.* This was vividly demonstrated by the work of Marsh and Waller,[19] who showed repeatedly that the hyperlipemia existing in patients with uncontrolled diabetes promptly disappeared as the diabetes became controlled, even though concurrently the fat of the diet was progressively increased from 85 to over 200 Gm. That controlling the diabetes is the important factor in eliminating hyperlipemia is likewise splendidly shown by the work of Curtis, Sheldon and Eckstein.[20] These investigators controlled severe diabetes in a boy *on a diet rich in fat* and measured the steady decline in the lipoids from 14 to 1.4 per cent. Then, keeping the fat of the diet constant *at 300 Gm.,* they allowed the diabetes to become uncontrolled by omitting insulin. Hyperglycemia, intense glycosuria and ketonuria developed, and simultaneously hyperlipemia occurred. All these abnormalities promptly disappeared when the diabetes was again controlled by the use of insulin.

At the beginning of this article reference was made to the fall in the average cholesterol values for the patients in Joslin's clinic during the past twenty years. That diabetes is better controlled now than in previous decades is shown in many ways, probably most strikingly by the huge decrease in the deaths due to coma. Joslin's statistics show that only 6.1 per cent of his patients died in diabetic coma between 1930 and 1935, as against 60.8 per cent between 1898 and 1914. It is our opinion that rather than explain the decrease in the average cholesterol value during the past two decades by the change to diets with lower fat and a higher carbohydrate content it would be more correct to explain the decrease on the basis of the greater success in controlling the disease.

19. Marsh, P. L., and Waller, H. G.: The Relation Between Ingested Fat and the Lipemia of Diabetes Mellitus, Arch. Int. Med. **31**:63 (Jan.) 1923.

20. Curtis, A. C.; Sheldon, J. M., and Eckstein, H. C.: Experimental Reproduction of Lipemia, Am. J. M. Sc. **186**:548 (Oct.) 1933.

CONCLUSIONS

In twenty-one patients with *controlled* diabetes who were on diets rich in fat for from two months to eight years, the cholesterol values of the blood during fasting were found to range between 126 and 223 mg. per hundred cubic centimeters, the average being 176 mg. In the same number of normal control subjects the values ranged between 130 and 186 mg. per hundred cubic centimeters, the average being 156 mg.

The level of cholesterol in the blood of these diabetic patients could not be correlated with the amount of fat in the diets.

Values only *slightly* higher than the highest ones for the control subjects were found in eight of the twenty-one subjects. The significance of these higher values is not clear.

Lack of control of the diabetes appears to be the major factor in the causation of hypercholesteremia in diabetic patients.

PNEUMOCOCCUS TYPE II AND TYPE V INFECTIONS

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The separation of types among the pneumococci previously included in group IV [1] has made it possible properly to classify pneumococci from practically all sources,[2] thus affording a more rational attack on various epidemiologic,[3] immunologic [4] and clinical [5] aspects of pneumo-

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1. (*a*) Cooper, G.; Edwards, M., and Rosenstein, C.: The Separation of Types Among the Pneumococci Hitherto Called Group IV and the Development of Therapeutic Antiserums for These Types, J. Exper. Med. **49**:461, 1929. (*b*) Cooper, G.; Rosenstein, C.; Walter, A., and Peizer, L.: The Further Separation of Types Among the Pneumococci Hitherto Included in Group IV and the Development of Antisera for These Types, ibid. **55**:531, 1932.

2. (*a*) Raia, A.; Plummer, N., and Shultz, S.: New Types of Pneumococci in the Pneumonias of Children, Am. J. Dis. Child. **42**:57 (July) 1931. (*b*) Gundel, M., and Seitz, L.: Die Pneumokokkentypen in der gesunden Bevölkerung, Klin. Wchnschr. **12**:929, 1933. (*c*) Bullowa, J. G. M.; Sommers, M., and Turner, E.: The Reliability of Sputum Typing and Its Relation to Serum Therapy, J. A. M. A. **105**:1512 (Nov. 9) 1935.

3. (*a*) Webster, L. T., and Hughes, T. P.: The Epidemiology of Pneumococcus Infection: The Incidence and Spread of Pneumococcus in the Nasal Passages and Throats of Healthy Persons, J. Exper. Med. **53**:535, 1931. (*b*) Smillie, W. G.: The Epidemiology of Lobar Pneumonia: A Study of the Prevalence of Specific Strains of Pneumococci in the Nasopharynx of Immediate Family Contacts, J. A. M. A. **101**:1281 (Oct. 21) 1933. (*c*) Gundel and Seitz.[2b]

4. Winkler, A. W., and Finland, M.: Antibody Response to Infections with the Newly Classified Types of Pneumococci (Cooper), J. Clin. Investigation **13**:109, 1934.

5. Sutliff, W. D., and Finland, M.: The Significance of the Newly Classified Types of Pneumococci in Disease: Types IV to XX Inclusive, J. A. M. A. **101**: 1289 (Oct. 21) 1933.

coccic infections and their specific treatment.[6] It has made possible also the segregation of pneumococci previously recognized primarily because of their relationship to other types.[7] The antibody response to infections with such related types and the immunologic reactions of normal human subjects to these pneumococci have already received some attention.[8] The clinical and bacteriologic features of the disease produced by type III and the related type VIII pneumococci have been reported from two different clinics.[9] This paper deals with the more important features of infections with type II and the related type V pneumococci, with especial reference to pneumonia.

The type II pneumococcus ranks second or third in frequency as a cause of pneumonia. The actual incidence in different series of cases of pneumococcic lobar pneumonia has varied from 10.9 per cent [10] to 32.7 per cent,[11] with a mortality rate of from 30 to 49 per cent in large

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6. Bullowa, J. G. M.: (*a*) The Therapeutic Value of Specific Type VII (Cooper) Antipneumococcus Serum, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 283; (*b*) Pneumonias Due to Pneumococcus Type VIII, Am. J. M. Sc. **190**:65, 1935; (*c*) Pneumonia Due to Pneumococcus Type XIV (Cooper) and Its Treatment with Specific Serum, J. Clin. Investigation **14**:373, 1935.

7. Avery, O. T.: A Further Study on the Biological Classification of Pneumococci, J. Exper. Med. **22**:804, 1915. Sugg, J. Y.; Gaspari, E. L.; Fleming, W. L., and Neill, J. M.: Studies on Immunological Relationships Among the Pneumococci: I. A Virulent Strain of Pneumococcus Which Is Immunologically Related to, But Not Identical with, Typical Strains of Type III Pneumococci, ibid. **47**:917, 1928. Harris, A. L.; Sugg, J. Y., and Neill, J. M.: Studies on Immunological Relationships Among the Pneumococci: II. A Comparison of the Antibody Responses of Mice and of Rabbits to Immunization with Type III Pneumococci and to Immunization with a Related Strain, ibid. **47**:933, 1928. Cooper, Edwards and Rosenstein.[1a]

8. (*a*) Finland, M., and Winkler, A. W.: Antibody Response to Infections with Type III and the Related Type VIII Pneumococcus, J. Clin. Investigation **13**:79, 1934; (*b*) Antibody Responses to Infections with Type II and the Related Type V Pneumococci, ibid. **13**:97, 1934. (*c*) Finland, M., and Sutliff, W. D.: Immunity Reactions of Human Subjects to Strains of Pneumococci Other Than Types I, II and III, J. Exper. Med. **57**:95, 1933.

9. (*a*) Finland, M., and Sutliff, W. D.: Infections with Pneumococcus Type III and Type VIII: Characterization of Pneumonia Caused by Pneumococcus Type III and That Associated with a Biologically Closely Related Organism, Pneumococcus Type VIII, Arch. Int. Med. **53**:481 (April) 1934. (*b*) Bullowa.[6b]

10. Thomas, W. S.: Type I Pneumonia and Its Serum Treatment, J. A. M. A. **77**:2101 (Dec. 31) 1921.

11. Griffith, F.: Serological Types of Pneumococci in Lobar Pneumonia: A Study of One Hundred Cases, Lancet **2**:226, 1921.

groups of patients who did not receive serum treatment.[12] This type has been said to give rise, with great regularity, to the typical clinico-anatomic picture of lobar pneumonia,[13] as distinguished from the so-called atypical forms[14] or bronchopneumonia. It is uncommon in pneumonia of childhood.[2a] Type II is rarely present in the normal nasopharynx except in persons who have come in contact with patients suffering from pneumonia due to this type.[15] It is likewise uncommon in cases of focal infection in the absence of pneumonia.[5] It is of added importance because there is evidence to indicate that patients with pneumonia due to this type of pneumococcus are benefited by the proper use of homologous antiserum.[16]

The type V pneumococcus is the most frequent and the most pathogenic of the types of pneumococci formerly recognized by their atypical reactions with type II antiserum.[17] In the past many instances of type V infection have probably been classified with cases of type II infection, a matter of some consequence, particularly in the evaluation of specific serum therapy. With the more accurate identification by means of specific agglutinating serums, the type V pneumococcus has been shown to be one of the most frequent of the new types present in cases of pneumonia.[18] It rarely occurs in the normal nasopharynx.[3] It was considered to be the causative agent in an institutional outbreak of colds, bronchitis and pneumonia.[19] Strains of this type have a greater tendency than others to hemolyze blood cells added to broth culture mediums, which may explain the large percentage of positive results of blood cultures in cases of type V infection.[1b]

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12. (*a*) Park, W. H.; Bullowa, J. G. M., and Rosenblüth, M. B.: The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, J. A. M. A. **91**:1503 (Nov. 17) 1928. (*b*) Cecil, R. L., and Plummer, N.: Pneumococcus Type II Pneumonia: A Clinical and Bacteriological Study of One Thousand Cases, with Especial Reference to Serum Therapy, ibid. **98**:779 (March 5) 1932.

13. Gundel, M.: Die Bakteriologie, Epidemiologie und spezifische Therapie der Pneumokokkeninfektionen des Menschen unter besonderer Berücksichtigung der Pneumonie, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **12**: 133, 1931.

14. Cole, R. I.: Acute Pulmonary Infections, De Lamar Lectures, 1927-1928, Baltimore, Williams & Wilkins Company, 1928.

15. Smillie.[3b] Gundel and Seitz.[2b]

16. (*a*) Finland, M., and Sutliff, W. D.: The Specific Serum Treatment of Pneumococcus Type II Pneumonia, J. A. M. A. **100**:560 (Feb. 25) 1933. (*b*) Cecil and Plummer.[12b] Other writers have reported similar results.

17. Stillman, E. G.: A Study of Atypical Type II Pneumococci, J. Exper. Med. **29**:251, 1919. Avery.[7]

18. Cooper and others.[1b] Bullowa, Sommers and Turner.[2c] Sutliff and Finland.[5]

19. Schroder, M. C., and Cooper, G.: An Epidemic of Colds, Bronchitis and Pneumonia Due to Type V Pneumococci, J. Infect. Dis. **46**:384, 1930.

PATIENTS INVESTIGATED AND SOURCES OF PNEUMOCOCCI

Since November 1929 all pneumococci obtained at the Boston City Hospital from sputum, blood or pus or from various sources at autopsy were classified with the aid of the new typing serums [1] obtained from Dr. William H. Park and Miss Georgia Cooper. For rapid typing of sputum the Sabin method [20] and, during the last two years, the *Quellung* reaction of Neufeld [21] have been utilized. These were checked as a routine by standard methods.[22] Strains of type II and type V pneumococci were cross-agglutinated in serums of both these types before they were definitely classified. Between Nov. 1, 1929, and May 31, 1935, pneumococci were obtained from a total of 2,950 patients. Type II pneumococci were obtained during this period from 263 patients and type V from 162 patients, an incidence

TABLE 1.—*Conditions Associated with Type II and Type V Pneumococci at the Boston City Hospital, November 1929 to May 1935*

	All Cases				Autopsies			
	Type II Pneumococci		Type V Pneumococci		Type II Pneumococci		Type V Pneumococci	
Disease	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Lobar pneumonia	219	83.3	107	66.0	38	71.7	22*	47.8
Bronchopneumonia	15	5.7	33	20.4	10	18.9	20	43.5
Empyema (present at entry)	12	4.6	6	3.7	..	....	1	2.1
Infections without pneumonia								
Otitis media and/or mastoiditis	4		4		1		1	
Meningitis	1		2		1		1	
Osteomyelitis	2		..		..		..	
Peritonitis	..		3		..		..	
Abscess of neck	1		..		..		..	
Bacteremia (no focus found)	3		..		3		..	
Pulmonary abscess	..		1		..		1	
Total	11	4.2	10	6.2	5	9.4	3	6.5
Infection of the upper respiratory tract	4	1.5	2	1.2	..	...	..	...
Pulmonary tuberculosis	2	0.8	2	1.2	..	...	..	...
Routine nasopharyngeal cultures	..	...	2	1.2	..	...	..	...
Total number of cases	263	100.0	162	100.0	53	100.0	46	100.0

* In 3 of these cases there was also some patchy infiltration in other portions of the lung.

of 8.2 and 5.5 per cent, respectively, of all cases of pneumococcic infection. Autopsies were performed in 53 of the cases of type II and in 46 of the cases of type V infection. The hospital records, roentgenograms and autopsy protocols were all utilized and correlated with the bacteriologic observations. Permission to use the bacteriologic and pathologic data was granted by Drs. Frederic Parker Jr. and Robert N. Nye, of the Mallory Institute of Pathology.

20. Sabin, A. B.: Microscopic Agglutination Test in Pneumonia, J. Infect. Dis. **46**:469, 1930.

21. Sabin, A. B.: Immediate Pneumococcus Typing Directly from Sputum by the Neufeld Reaction, J. A. M. A. **100**:1584 (May 20) 1933.

22. Avery, O. T.; Chickering, H. T.; Cole, R., and Dochez, A. R.: Acute Lobar Pneumonia: Prevention and Serum Treatment, Monograph 7, Rockefeller Institute for Medical Research, 1917.

The conditions which could be attributed to the type II and V pneumococci are listed in table 1. The intimate association of both these types with pneumonia is apparent. In 93.6 per cent of the patients with type II pneumococci and in 90.1 per cent of those with type V pneumococci there was either pneumonia or empyema attributed to these organisms.

CONDITIONS OTHER THAN PNEUMONIA

The pneumococci from the patients with infection of the upper respiratory tract and from the patients with pulmonary tuberculosis, noted in table 1, were obtained from the sputum. A case of tonsillitis with type II pneumococci is included among the former cases. Tubercle

TABLE 2.—*Focal Infections with Type II and Type V Pneumococci*

Case	Sex	Age, Years	Focal Infection	Outcome	Remarks*
				Type II Infection	
1	F	4	Mastoiditis	Died	S Au from other ear and meninges
2	M	23	Mastoiditis	Died	Also S H sepsis
3	M	4	Otitis media	Lived	
4	F	9	Mastoiditis	Lived	After scarlet fever
5	M	56	Meningitis	Died	Pn II bacteremia; treated with Felton's serum
6	M	70	Abscess of neck	Died	
7	M	14	Osteomyelitis	Lived	Began as cellulitis
8	F	3	Osteomyelitis	Lived	S Au cultured before
				Type V Infection	
1	M	1	Mastoiditis	Died	After scarlet fever; S H in blood and other ear
2	F	6	Otitis media	Died	S H in blood and meninges
3	F	2	Mastoiditis	Lived	
4	M	5	Mastoiditis	Lived	
5	F	8	Meningitis	Died	After otitis media
6	M	8	Meningitis	Died	
7	M	55	Lung abscess	Died	Also S Au and B. coli; in carcinoma of lung
8	M	2	Peritonitis	Lived	With appendicitis
9	F	44	Peritonitis	Lived	With pyosalpynx
10	M	11	Peritonitis	Lived	Ruptured appendix

* For the key to the abbreviations see table 4.

bacilli were demonstrated in the sputum of all but 1 (also a case of type II infection) of the 4 tuberculous patients, none of whom gave definite evidence of any acute infection which could be attributed to the pneumococci. In 2 patients type V pneumococci were obtained from the nasopharyngeal cultures made as a routine, for hemolytic streptococci in one instance and for diphtheria bacilli in the other. Neither of these patients had an active infection. There were no deaths among this group of patients.

In the patients admitted to the hospital with empyema and in those with focal infection the pneumococci were isolated from cultures of pus obtained directly from the lesions. In the 3 cases of so-called bacteremia the pneumococci were obtained from cultures of the heart blood made at autopsy. One of these patients was a premature infant who died as a

result of progressive jaundice and diarrhea; the second was a 2 month old infant with congenital syphilitic cirrhosis of the liver and jaundice, and the third was a woman of 60 who died shortly after being admitted to the hospital because of a relapse of pernicious anemia. In none of these 3 patients was any evidence of infection present in any organ.

All the patients who had empyema at the time of admission to the hospital were treated with open drainage by rib resection. Death occurred in 2 such cases of type II infection in patients aged 83 and 27 years, respectively, and in 2 cases of type V infection in patients aged 80 and 47 years, respectively. The fatal cases were all in males. Of the surviving patients with empyema due to type II pneumococci, 7 were less than 15 years old and the others were aged 21, 42 and 50 years, respectively. Only 1, an infant, was a female; the others were males. The patients with empyema due to type V pneumococci who recovered, 1 male and 3 females, were all under 14 years of age.

Some of the features in the cases of other purulent focal infections are listed in table 2. Other organisms were often cultured from material from the same patient, streptococci and staphylococci being the most common. The deaths in the cases of infection of the middle ear and of the mastoid were probably due to invasion by streptococci.

The remainder of this paper will be devoted to a consideration of the clinical and bacteriologic aspects and pathologic observations of the pneumonia associated with type II and V pneumococci. Specific antiserum was used in some of the cases of type II infection which were therefore segregated in calculating mortality percentages. The effects of serum therapy are analyzed elsewhere.[23]

PNEUMONIA DUE TO TYPE II AND TYPE V PNEUMOCOCCI

The sources from which the type II and type V pneumococci were obtained in the cases of pneumonia are noted in table 3. In half the patients with pneumonia these pneumococci were obtained from sources other than the sputum, which indicated a definite etiologic relationship to this disease. In about one fifth of the patients in whom the sputum was the only source of the pneumococcus the same type was obtained from 2 or more specimens. In all, type II pneumococci were identified in 524 specimens and type V in 319 specimens of various materials obtained from patients with pneumonia.

MIXED INFECTIONS

The clinical significance of isolating pneumococci of more than one type or of isolating pneumococci and other significant organisms from

23. (*a*) Finland, M., and Dowling, H. F.: The Dose of Antibody Effective in the Treatment of Pneumococcus Type II Pneumonia, Am. J. M. Sc. **191**:658 (May) 1936. (*b*) Finland and Sutliff.[16a]

patients with pneumonia has been discussed elsewhere.[24] Immunologic studies have indicated that some pneumococci, particularly types I and II, when they are obtained in cases of pneumonia along with other types of pneumococci, are more likely to be the significant etiologic agent than others, particularly type III pneumococci. In the present series other types of pneumococci were obtained from 4 of the patients with type II pneumonia and from 7 of the patients with type V pneumonia, an incidence of 1.7 and 5 per cent, respectively. All other significant organisms, including pneumococci, were found in 20 of the cases of type II pneumonia and in 21 of the cases of type V pneumonia, constituting 8.5 and 15 per cent, respectively, of the cases of pneumonia due to these types.

TABLE 3.—*Sources of Type II and Type V Pneumococci Obtained in Cases of Pneumonia*

Source	Type II		Type V	
	Cases	Per Cent	Cases	Per Cent
Single specimen of sputum	97	41.4	55	39.3
Multiple specimens of sputum	27	11.5	15	10.7
Blood or pus	11	4.7	15	10.7
Autopsy	17	7.3	20	14.3
Autopsy and antemortem cultures	21	9.0	17	12.1
Multiple sources during life	61	26.1	18	12.9
Total	234	100.0	140	100.0
At autopsy				
Heart blood	23		21	
Lungs	31		30	
Pus (all foci)	17		17	
No cultures made	8		5	

A study of the sources of the various organisms listed in table 4 indicates that the rôle of other pneumococci, when found with either type II or type V strains, was probably a minor one. Further evidence for such an assumption was adduced from immunologic studies in some of these cases which indicated that only the type II or V pneumococci were antigenically active.[8b] Streptococci and staphylococci, on the other hand, were usually secondary invaders causing "superinfections," although in some instances, when they were obtained only from the sputum, they were probably not related to the pulmonary infection. The rôle of Haemophilus influenzae was difficult to evaluate. The patients with tubercle bacilli noted in table 4 all had typical lobar pneumonia complicating active pulmonary tuberculosis, in contrast to the cases noted in table 1 in which there was no acute infection attributable to the pneumococcus.

24. Finland, M.: The Significance of Mixed Infections in Pneumococcic Pneumonia, J. A. M. A. **103**:1681 (Dec. 1) 1934. Winkler and Finland.[4]

TABLE 4.—*Mixed Infections in Cases of Pneumonia Due to Type II and Type V Pneumococci*

Case	Pneumonia* Kind	Outcome	Sources of Homologous Type of Pneumococcus†	Other Organisms‡	Sources
Type II infection					
1	L	R-6	S-3, 4; B-3	B M C	S-3, 4
				Pn IV	S-11, 12
2	L	D-10	S-6; Peric.	Pn III	Rll
3	B	R-5	S-3	Pn III	S-3
4	L	D-9	B-7	Pn XX	S-8
5	L	D-?	Rll	S H	Rll
6	L	D-7	S-3; B-3	S H	S-6
7	L	D-7	S-3; B-3, 6; H; all lobes	S H	Lul
8	B	D-?	Lll	S H	H; Lll
9	B	D-2	Rll; Lll	S H	Rll; Lll
10	B	D-7	Rll	S H	Rll; Rul; Lll
11	L	R-6	S-5	S Au	Cervical abscess-17
12	L	R-?	S-2; B-3	S Au	S-21, 36; B-6, 9; ear-10, 19
				S H	B-18; ear 19; C 22, 23
13	L	R-7	S-3	S H; S Au	Ear-17
14	B	D-3	S-1	S H; S Au	S-1
15	L	R-17	S-16	H I	S-15
16	L	D-10	S-6; B-6; H; Rll; Lll	H I	Rll; Lll
17	L	D-12	S-3; B-3, 8, 10; 4 lobes	S V	3 lobes (1 without Pn II)
18	L	R-8	S-6; B-7	T B	6 times
19	L	R-14	S-11	T B	4 times
20	L	R-17	S-17	T B	3 times
Type V infection					
1	L	R-6	S-5	Pn III	S-9
2	L	R-8	S-13, 16	Pn III; H I	S-11
3	L	D-33	S-9; C-16, 23, 30	Pn X	S-6
4	L	D-4	S-4; H; C; Rll; Rul; Lll	Pn X	Lll
5	L	R-8	S-30	Pn XI	S-3
6	B	D-12	Rll	Pn XIV	S-2, 3
7	B	D-12	Rll; Lll	XVIII; S H	S-8
8	L	D-11	S-6, 10; B-6, 10; C (Rt.)	S H	Abd; C (left)
9	B	D-12	Mastoid	S H	B-7, 9; H
10	L	R-?	S-4; B-4	S H	C-16; throat-21
11	L	D-13	S-12	S H	S-6
12	B	D-?	Rll	S H; B. coli	Lll
13	B	D-11	S-1, 7; B-7, 8	S H	B-10
14	L	R-?	C-15, 17, 30, 38, 42	S Au	Throat-7, 8
15	L	R-?	C-9, 12, 17	S H; S Au	C-21
16	L	R-16	S-14	S H; S Au	S-15
17	B	D-2	S-1	S H	H; Rll; C; Abd.
				S Au	Rll; C
				B. coli	Abd.; kidney
18	L	D-6	Rll	S H	H; Rll
				S Au	Rll
19	B	R-4	S-3	H I	S-3
20	B	D-16	S-5, 6, 7; Rll	H I	S-5, 6, 7
21	L	D-19	S-14	S H; H I	Rll

* L indicates lobar pneumonia; B, bronchopneumonia; R, recovered, and D, died, and the numbers represent the day of the disease on which the study was made.

† S indicates sputum; B, blood; C, pleural exudate; Rll, lower lobe of right lung; Lll, lower lobe of left lung; Rul, upper lobe of right lung; Lul, upper lobe of left lung; Peric, pericardial exudate; Abd., peritoneal exudate, and H, heart blood, and the numbers represent the day of the disease. When no number is given, the cultures were made at autopsy.

‡ Pn indicates pneumococcus (type is given in Roman numerals); B M C, Bacillus mucosus capsulatus; S H, beta hemolytic streptococcus; S Au, hemolytic Staphylococcus aureus; H I, Haemophilus influenzae; S V, Streptococcus viridans, and T B, tubercle bacilli (sputum smears).

SEASONAL INCIDENCE

The month of the highest incidence, as noted with regard to type III and type VIII pneumonia,[9a] differed from year to year. It always occurred between January and March. It was usually the same for type II as for type V pneumonia and corresponded to the month when types I, III and VIII pneumonia also were most frequent. In some years there was more than a proportionate number of cases of one type or another during the peak month. During some months, also, there was a disproportionate increase in the number of cases of one type independent of the general peak of incidence. The largest number of patients with each type of pneumonia admitted in any one month was 17 with type II pneumonia in March 1932 and 12 with type V pneumonia in January 1933. The annual incidence showed decided variations (table 5), although the total number of cases of pneumococcic pneumonia for each year was fairly constant over the period of this study.

TABLE 5.—*Annual Incidence of Infections Due to Type II and Type V Pneumococci*

	All Cases		Pneumonia and Empyema	
Year	Type II	Type V	Type II	Type V
1929-1930	51	13	48	13
1930-1931	60	20	56	19
1931-1932	55	17	52	16
1932-1933	54	55	47	50
1933-1934	25	31	25	25
1934-1935	18	26	18	23
All years	263	162	246	146

AGE AND SEX INCIDENCE WITH RELATION TO MORTALITY

The number of patients with type II and type V pneumonia, arranged according to age and sex, are shown in table 6. The mortality in each group is noted. The patients under 10 years of age are not comparable with the rest of the patients since no special effort was made to study them bacteriologically. The type of pneumococcus in these cases was determined only from organisms obtained from the blood, pleural fluid or autopsy materials. Partly for this reason and partly also because a number of infants were included, the percentage mortality in this age group is inordinately high. Briefly, the age distribution was closely similar in the cases of type II and of type V lobar pneumonia, except for the greater incidence of children under 10 years of age. The mortality figures for the cases of type V pneumonia also show a striking similarity, within the various age groups, to those found in the cases of

type II pneumonia in which serum was not given. There was a distinctly smaller proportion of females among the patients with type II pneumonia than among those with type V pneumonia. The mortality rate was the same among males and females in each group.

COMPARISON OF THE INCIDENCE AND MORTALITY IN LOBAR PNEUMONIA AND BRONCHOPNEUMONIA DUE TO TYPE II AND TYPE V PNEUMOCOCCI

Particular care has been taken throughout this study to classify the cases of pneumonia according to the character of the lesion in the lung.

TABLE 6.—*Analysis of Incidence and Mortality of Pneumonia Due to Type II and Type V Pneumococci*

	Lobar Pneumonia												Bronchopneumonia							
	Type II								Type V				Type II				Type V			
	Serum			No Serum			All													
Cases Age, Years	Number	Died	Died, per Cent	Number	Died	Died, per Cent	Incidence, per Cent		Number	Died	Died, per Cent	Incidence, per Cent	Number	Died	Died, per Cent	Incidence, per Cent	Number	Died	Died, per Cent	Incidence, per Cent
All cases	86	27	31	133	64	48	94†		107	46	43	74†	15	12	80	6†	33	24	73	26†
<10 years*	..	..	..	..	..	..	0		4	1	25	4	3	2	..	20	6	5	..	18
10-19 years	13	1	8	13	1	8	11		12	1	8	11	1	1	..	7	2	0	..	6
20-29 years	21	4	19	22	8	36	20		16	5	31	15	0	0	..	0	2	2	..	6
30-39 years	21	7	33	27	7	26	22		28	8	29	26	3	2	..	20	4	2	..	12
40-49 years	15	5	33	29	18	62	20		17	9	53	16	1	0	..	7	6	6	..	18
50-59 years	14	8	57	22	14	64	16		17	11	65	16	2	2	..	13	3	1	..	9
60-69 years	3	2	67	16	12	75	9		9	7	78	8	2	2	..	13	7	6	..	21
70+	..	..	..	4	4	100	2		4	4	100	4	3	3	..	20	3	2	..	9
Males	73	24	33	111	51	46	84		76	32	42	71	13	11	85	87	19	13	79	58
Females	13	3	23	22	13	59	16		31	14	45	29	2	1	50	13	14	11	68	42
Primary	82	23	28	126	60	48	95		100	42	42	93	1	1	100	7	14	10	71	42
Secondary	4	4	100	7	4	57	5		7	4	57	7	14	11	79	93	19	14	74	58
Mixed infections	6	4	67	9	3	33	7		13	6	46	12	5	4	80	33	8	7	88	24

* Study limited to medical cases (patients over 12 years of age). The bacteriologic data were available for only a small number of the patients less than 12 years of age.

† Per cent of all cases of pneumonia of this type. Other percentages refer to lobar or bronchopneumonia.

In this respect, the autopsy observations, when available, were considered the most significant, and the roentgen and physical findings, in the order mentioned, were considered next in importance. Only rarely, however, were the findings in disagreement. For purposes of classification all cases in which the pulmonary lesion was atypical, that is, not uniform in distribution, were called instances of bronchopneumonia. The relative frequency with which such cases were encountered is shown in table 6. In addition, the numbers of cases are listed in this table according to age, sex, primary and secondary pneumonia and mixed infections. The percentage of incidence and of mortality is noted for each group.

Atypical pneumonia is relatively more common among patients with type V pneumococcic pneumonia than among those with type II pneumonia, about 1 in every 4 of the former and 1 in every 16 of the latter having bronchopneumonia. There was a greater percentage of persons over 60 years of age with bronchopneumonia than with lobar pneumonia. The mortality among the patients with bronchopneumonia varied only slightly with age, whereas among the patients with lobar pneumonia the mortality showed the usual increase with advancing age. Except among persons over 60 years of age, the mortality was always higher among the patients with bronchopneumonia. This greater number of deaths is due, in large part, to the fact that in most cases bronchopneumonia was secondary to some other serious acute disease, while in most cases of lobar pneumonia the pneumonia was primary. There were relatively more female patients among those with type V bronchopneumonia than among those with lobar pneumonia. Mixed infections were more common and associated with a higher mortality among the patients with bronchopneumonia.

PREDISPOSING FACTORS

Some of the common conditions within the patient which may be considered as predisposing to pneumonia or affecting its course are listed in table 7. It is seen from this table that the cases of type II and type V pneumonia were closely similar with respect to the incidence of these conditions and their effect on the mortality. The findings with respect to these factors may be summarized briefly.

Secondary Pneumonia.—Under this term are included those cases in which the onset of pneumonia occurred in the course of a severe acute illness or during an acute episode in a chronic illness. Postoperative pneumonia also was included. Congestive cardiac failure and acute infections, notably measles and pertussis in children, were the commonest primary conditions. Bronchopneumonia was predominantly secondary, whereas in only a small percentage of the cases was lobar pneumonia secondary to some other condition. The various primary conditions are noted in the table and in the footnotes.

Alcoholism.—All patients from whom a history of alcoholic habits could be obtained were classified arbitrarily in three groups. The first group includes those who denied using alcoholic beverages or who rarely partook of small amounts; these are termed abstainers. The second group includes patients who regularly took small or moderate amounts; they are called mild or moderate chronic alcoholic patients. In the last category are considered those who were chronically addicted to the use of alcohol, who were acutely intoxicated or who had delirium tremens

in the course of pneumonia. The progressively greater mortality in these three groups of patients is apparent from table 7.

Acute Infection of the Respiratory Tract.—In about half the patients from whom a history was elicited in this regard some simple acute

TABLE 7.—*Incidence of Common Predisposing Factors in Cases of Pneumonia Due to Type II and Type V Pneumococci* *

		Type II Pneumonia								Type V Pneumonia							
		Lobar Pneumonia				Broncho-pneumonia				Lobar Pneumonia				Broncho-pneumonia			
		Recovered	Died	Mortality, per Cent	Incidence, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent
1. Primary conditions in cases of secondary pneumonia																	
Cardiac failure		1	4[a]	..	..	..	4[b]	..	..	..	3	..	..	1	5	..	..
Acute infection		..	..	..	..	1[c]	2[d]	..	..	1[e]	..	..	..	2[f]	5[g]	..	..
Fracture		..	2[h]	..	..	1[i]	..	..	..	..	..	..	..	1[h]	..	..	..
Cancer (terminal)		..	..	..	..	..	2[j]	..	..	..	..	..	..	..	2[k]	..	..
Operation		1[l]	..	..	..	1[m]	..	..	..	1[n]	..	..	..	..	2[o]	..	..
Other conditions		1[p]	2[q]	..	..	..	3[r]	..	..	1[s]	1[q]	..	..	1[t]	2[u]	..	..
Total		3	8	73	5	3	11	79	93	3	4	57	7	5	16	76	64
2. Alcoholism																	
Abstainers	Serum	29	6	17	50	..	..	..	..	..	..	..	..	..	..	..	..
	No serum	32	12	28	48	..	2	..	..	21	8	27	47	3	7	70	58
Mild to moderate, chronic	Serum	18	8	31	37	..	..	..	..	..	..	..	..	..	..	..	..
	No serum	16	18	53	37	1	1	..	..	12	9	43	34	1	4	80	26
Acute and/or delirium tremens	Serum	4	5	55	13	..	..	..	..	..	..	..	..	..	..	..	..
	No serum	4	10	71	15	..	1	..	..	5	7	58	19	2	2	50	21
3. Antecedent acute infection of upper respiratory tract [v]																	
Present	Serum	34	16	32	60	1	0	..	..	..	..	..	..	..	..	..	..
	No serum	45	24	45	42	2	2	50	50	24	14	37	43	3	11	79	67
Absent	Serum	23	10	30	40	..	..	..	..	..	..	..	..	..	..	..	..
	No serum	61	34	44	58	0	4	100	50	29	22	43	57	3	4	71	33
4. Other conditions not directly related to onset of pneumonia [v]																	
Chronic cardiac disease		2	7[a]	..	..	..	..	..	..	1	3	..	..	..	..	..	..
Chronic pulmonary infections		7	6	..	..	..	..	..	..	4	3	..	..	..	3	..	..
Pregnancy		2	..	..	..	..	..	..	..	..	2	..	..	..	1	..	..
Diabetes		2[w]	..	..	..	..	..	..	..	1	1	..	..	..	1	..	..
Antecedent otitis media		1	..	..	..	..	..	..	..	5	..	..	..	..	..	..	..
Acute urethritis		3	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..
Others		4[x]	..	..	..	..	..	..	..	2[y]	..	..	..	..	..	..	..
Total		21	14	40	16	0	..	..	..	14	9	39	21	0	5	100	15

* The significance of the superior letters used in the columns is as follows: a indicates 1 with cirrhosis of liver; b, 1 with cirrhosis and asthma; 1 with diabetes; c, measles; d, measles 1, scarlet fever and encephalitis 1; e, scarlet fever 1, pyelitis 1; f, scarlet fever; g, measles 1, pertussis 1, acute cholecystitis 1; h, ribs 1, skull 1; i, ribs; j, mouth 1, lung 1; k, both—cancer of lung with necrosis; l, peritonitis; m, bone flap for epilepsy; n, parturition; o, cholecystogastrostomy 1, ruptured appendix 1; p, hemoptysis (tuberculous); q, parturition; r, abscess of lung 1, cerebral thrombosis 1, coronary thrombosis 1; s, diabetic acidosis; t, cerebral thrombosis; u, acute psychosis with ingestion of iodine 1, pulmonary infarct 1; v, incidence is given as percentage of those with definite history; w, 1 with acute otitis media; x, bronchial asthma 2, convalescent from catarrhal jaundice 1, furunculosis 1, and y, secondary anemia, including 1 post partum.

infection of the upper respiratory tract, including the common cold, pharyngitis, grip, influenza and bronchitis, was present within two weeks preceding the onset of pneumonia. The mortality was the same among the patients with and those without such an antecedent infection.

Other Conditions.—Under this heading in the table are listed focal infections and chronic diseases which were not considered to be directly related to the onset of pneumonia. Such conditions were present in 16 and 21 per cent, respectively, of the patients with primary lobar pneumonia due to type II and type V pneumococci. The mortality among these patients was the same as that for the entire group.

CLINICAL FEATURES

It is of interest to compare some of the clinical characteristics of the pneumonia due to type II and that due to type V pneumococci.

TABLE 8.—*Symptomatology*

	Cases of Type II Pneumonia*		Cases of Type V Pneumonia			
			Lobar Pneumonia		Bronchopneumonia	
	Number	Per Cent†	Number	Per Cent†	Number	Per Cent†
Mode of onset						
Sudden	157	83	86	84	19	63
Gradual	33	17	16	16	11	37
Initial symptom						
Chill	77	47	36	36	3	11
Pain in chest	52	32	34	34	11	39
Chill and pain in chest	15	9	7	7	..	..
Chills, grip	3	2	9	9	6	22
Headache, weakness	8	5	4	4	1	4
Cough	3	2	3	3	5	18
Nausea, vomiting	3	2	3	3	..	..
Bloody sputum	2	1	1	1	..	..
Sore throat	1	0.6	1	1	..	..
Abdominal pain	..	..	3	3	1	4
Epistaxis	..	..	..	..	1	4
Cardinal features						
Chill	151	77	68	73	8	37
Chest pain	178	92	94	90	18	82
Rusty sputum	118	77	50	63	7	47
All three	89	60	34	36	4	20
Only two	48	30	33	35	5	25
Only one	14	9	23	24	11	55
None	2	1	4	4	0	0

* No reliable data were available in the cases of type II bronchopneumonia, because of the predominance of symptoms of other diseases.

† The percentage of incidence is figured on the basis of the cases in which a definite history was available on each point.

Some of the features in the histories of the patients and their frequency are listed in table 8. In the 15 patients with type II bronchopneumonia, in all of whom the condition was secondary, the symptomatology was related to the primary disease.

Mode of Onset.—There was an abrupt onset in the great majority of cases, especially in the cases of lobar pneumonia. The commonest initial symptoms were chill and pleuritic pain, one or both of these symptoms ushering in the disease in 88 and 77 per cent, respectively, of the cases of lobar pneumonia due to type II and type V pneumococci and in 50 per cent of the cases of bronchopneumonia due to type V pneumococci.

Cardinal Features.—Pleural pain was the most frequent symptom in all cases. A single chill and rusty or blood-tinged sputum, however, were more characteristic of the cases of lobar pneumonia. Either two or all three of these symptoms were present together in 90 per cent of the cases of type II and 71 per cent of the cases of type V lobar pneumonia, as compared with 45 per cent among cases of type V bronchopneumonia.

Extent of the Pulmonary Involvement.—The relation of the site and the extent of the pulmonary lesion to the mortality is shown in table 9. The proportion of the patients with lobar pneumonia showing various

TABLE 9.—*Extent of Pulmonary Involvement*

		Type II Pneumonia							Type V Pneumonia			
		Serum			No serum			All				
	Lobes Involved	Recovered	Died	Mortality, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent
Lobar pneumonia												
Right	Lower	17	2	..	14	13	..	21	15	5	..	19
	Upper and/or middle	7	2	..	12	0	..	14	7	8	..	14
	Lower and middle	5	0	..	4	6	..	7	4	3	..	7
	Upper and lower*	1	5	..	7	9	..	10	8	10†	..	17
Left	Lower	24	4	..	18	9	..	25	19	7	..	24
	Upper	0	0	..	2	2	..	2	0	1	..	1
	Upper and lower	1	2	..	6	2	..	5	3	4	..	7
Total 1 lobe*		53	8	13	50	40	44	69	45	24	35	64
Total 1 entire lung*		2	7	78	13	11	48	15	11	14	56	23
Bilateral	2 lobes	4	8	..	3	9	..	11	3	7	..	9
	3 lobes	0	0	..	2	2	..	2	1	0	..	1
	4 or 5 lobes	0	4	..	1	2	..	3	1	1	..	2
	Total bilateral	4	12	75	6	13	68	16	5	8	61	12
Bronchopneumonia												
Mostly unilateral		..	..	..	1	3	75	27	5	8	61	39
Bilateral		..	..	..	2	9	82	73	4	16	80	61

* With or without middle lobe.
† Three patients also had bronchopneumonia on the left side.

amounts of consolidation was closely similar among those with type II and those with type V pneumonia. In about two thirds of the patients with lobar pneumonia the consolidation was limited to a single lobe. As expected, the patients with the more extensive lesions showed a higher mortality than those with more limited involvement. It may be noted, in passing, that the only reduction in mortality following serum treatment occurred in cases in which the lesion was confined to one lobe.

Duration of the Disease.—The duration of acute symptoms, including a temperature of 101 F. and higher (by mouth), is given in table 10. It is worth noting that 44, or 76 per cent, of the patients with type II pneumonia who received serum treatment and who recovered were practically symptom-free by the end of the fifth day and 55, or 95 per

TABLE 10.—*Duration of the Disease*

Day of Disease	Type II Lobar Pneumonia*				Type V Pneumonia			
	Serum		No Serum		Lobar Pneumonia		Bronchopneumonia	
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died
1	3	0	0	0	0	0	0	0
2	5	0	1	1	0	1	0	2
3	12	2	0	2	1	1	2	2
4	13	3	6	2	3	7	3	1
5	11	4	6	8	7	4	2	5
6	6	2	5	11	10	4	0	1
7	5	7	11	5	7	4	0	1
8	0	2	15	3	11	7	1	1
9	1	1	5	10	5	1	0	1
10	1	1	3	8	5	3	0	0
11	0	0	2	2	1	1	0	0
12	1	2	4	1	2	1	0	2
13	0	1	2	4	0	1	0	1
14	0	0	3	0	1	0	0	1
15–21	0	0	4	0	3	4	0	2
22+	0	3	1	1	0	4	1	1
?	0	0	1	6	5	3	0	3
Total	58	28	69†	64	61‡	46	9	24

* The duration in type II bronchopneumonia could not be determined.
† Crisis in 34 cases (49 per cent); lysis in 35 cases (51 per cent).
‡ Crisis in 27 cases (44 per cent); lysis in 34 cases (56 per cent).

TABLE 11.—*Complications (Diagnosed During Life)* *

Complications	Type II Pneumonia				All 219 Cases	Type V Pneumonia, 140 Cases		
	Serum (86 Cases)		No Serum (133 Cases)					
	Recovered	Died	Recovered	Died	Incidence, per Cent	Recovered	Died	Incidence, per Cent
Empyema	3[a]	..	3[b]	2	3.6	9[c]	6[d]	10.7
Meningitis	..	..	..	4[e]	1.8	..	2	1.4
Pericarditis	..	..	..	..	...	..	1	0.7
Otitis media	2[f]	..	1[g]	1	1.8	3[g]	..	2.1
Sterile pleural effusion	3	..	4[i]	1	3.6	2[i]	1	2.1
Acute tonsillitis	2[h]	..	1	..	1.4	3	..	2.1
Pyelitis	1	..	..	..	0.5	..	..	0.7
Conjunctivitis	..	..	1	..	0.5	1	..	...
Acute nephritis	..	..	..	..	...	2	..	1.4
Subcutaneous abscesses	1[j]	..	1[k]	1	1.4	..	..	...
Miscarriage	1	..	1	..	0.9	..	1	0.7
Jaundice	4	2	5	2	5.6	1	2	2.1
Furunculosis	..	..	1[l]	..	0.4	..	..	...
Granulopenia	..	..	..	1	0.4	..	..	...
Meningismus	..	..	..	..	...	..	1	0.7
Air embolus	..	..	..	..	...	..	1	0.7
Thrombophlebitis	..	..	..	..	...	1	..	0.7
Auricular fibrillation	..	2	1	8[m]	5.0	..	2[n]	1.4
Delirium tremens	..	3	2	7[m]	5.5	1	2[m]	2.4
Atelectasis (roentgen diagnosis)	..	..	2	3	2.3	2	4	4.3
Extensions	1[o]	4[o]	6	5	7.3	6	12[p]	12.9

* The significance of the superior letters used in these columns is as follows: a indicates 1 with Str. haemolyticus on culture, and otitis media; b, bronchopneumonia 1, 1 also had pneumococcic conjunctivitis; c, bronchopneumonia with otitis media 1, acute nephritis and otitis media 1, Str. haemolyticus on culture 1; d, bronchopneumonia 2, pericarditis 1; e, bronchopneumonia 1, otitis media 1; f, Str. haemolyticus and Staph. aureus cultured from 1; g, jaundice 1; h, pyelitis 1; i, acute tonsillitis 1; j, miscarriage; k, no growth on culture; l, Staph. aureus; m, bronchopneumonia 1; n, both bronchopneumonia; o, all occurred in 1932-1935,[32a] and p, bronchopneumonia 4.

cent, were relieved after the seventh day of illness. Compared with these figures, only 19 per cent of the patients with type II pneumonia and 18 per cent of those with type V lobar pneumonia who did not receive serum treatment were free from fever and symptoms of acute infection by the end of the fifth day, and 42 and 46 per cent, respectively, were relieved after the seventh day.

TABLE 12.—*Bacteremia in Pneumonia Due to Type II and Type V Pneumococci; Incidence, Mortality and Relation to Age*

	Patients with Bacteremia					Patients Showing Sterile Blood Cultures				
	Type II*			Type V		Type II			Type V	
	Serum	No Serum	All	Lobar pneumonia	Broncho-Pneumonia	Serum	No Serum	All	Lobar Pneumonia	Broncho-pneumonia
Number of cases	30	53	83	31	11	47	39	86	48	12
Per cent incidence‡	39	58	49	40	48	61	42	51	60	52
Died	19	38	57	27	11	6	10	16	10	8
Per cent mortality	63	72	69	84	100	13	26	19	21	75
19 years or less										
Number	2	0	2	1	3†	9	9	18	8	1†
Per cent of age group	18	0	10	11	75	82	100	90	89	25
Died	1	0	1	0	3	0	0	0	1	1
Per cent mortality	50	..	50	0	100	0	0	0	13	100
20-39 years										
Number	14	17	31	10	3	24	18	42	23	2
Per cent of age group	37	49	42	30	60	63	51	58	70	40
Died	9	8	17	7	3	2	5	7	2	0
Per cent mortality	64	47	55	70	100	8	28	17	9	0
40-59 years										
Number	11	25	36	11	3	14	10	24	15	5
Per cent of age group	44	71	60	42	37	56	29	40	58	63
Died	7	21	28	11	3	4	4	8	6	4
Per cent mortality	64	84	78	100	100	29	40	33	40	80
60 years and older										
Number	3	11	14	10	2	0	2	2	2	4
Per cent of age group	100	85	87	83	33	0	15	13	17	67
Died	2	9	11	9	2	0	1	1	1	3
Per cent mortality	67	82	79	90	100	..	50	50	50	75

* Of the patients with bronchopneumonia 4 (aged 1, 50, 67 and 75 years) had bacteremia and 5 (aged 2, 5, 35, 50 and 56 years) showed sterile cultures, an incidence of 44 per cent for bacteremia.

† All under 1 year of age.

‡ Per cent of cases in which blood cultures were made.

Complications.—The complications noted during the course of the disease or during convalescence are listed in table 11. Empyema and extension of the pulmonary lesion were relatively more frequent among the patients with type V pneumonia, whereas delirium tremens and auricular fibrillation were more frequent among those with type II pneumonia.

TABLE 13.—*Course of Bacteremia in Relation to Outcome*

Case	Serum, Day*	Days After Onset: 2	3	4	5	6	7	8	9	10	11	12	13	14+
Type II; serum treatment														
1	4	..	B	1, 0	0	0, L	0	..	..	..	..	..	..	..
2†	3	..	3	0	SA	SA	..	..	..	..	..	..	..	SH
3	2	362	B	0	0, L	0	..	..	0	..	..	..	..	..
4	2	+, +, B	400, 88, 200, 1,000	D	..	..	..	..	..	..	..	..	..	..
5	3	..	B	0, C	..	..	..	..	..	..	..	..	..	..
6	3	..	B	0	0, 0	0, D	..	..	..	..	..	..	..	..
7	4	..	..	+	+	0	D	..	..	..	..	..	..	..
8	213	..	..	..	..	..	..	..	..	..	..	91	D	0
9	4	..	2,000	4,000	9, D	+	..	..	..	..	..	..	..	..
10	3	+	15	0	..	0	273	1, D	0	..	..	..	..	..
11	2	0	..	..	..	+	..	0	..	0	L	..	..	..
12	2	+	C	0	..	..	..	..	..	..	..	..	..	..
13	2	0	+	0	..	+	D	..	..	..	..	..	..	..
14	2	+	0, L	..	..	..	..	..	..	..	..	..	..	..
15	2	+	0	0	..	..	D	..	..	..	..	..	..	..
16	9	..	..	..	..	0	..	+	0	..	+	..	D	..
17	3	..	+	+, D	+	..	..	..	..	..	..	..	..	..
18	2	+	0	..	0	..	D	..	..	..	..	..	..	..
19	7	..	..	..	..	+	..	..	D, +	..	..	..	..	..
20	3	..	+	..	..	+	D, +	..	..	..	..	..	..	..
21	4	..	+	..	0	..	..	0	..	..	L	..	..	..
22	4	..	..	+	D	+	..	..	..	..	..	..	..	..
23	3	..	+	..	..	0	..	..	+	..	+	..	D	0
24	2	0	..	+	D	+	..	..	..	..	..	..	..	..
Type II; no serum treatment														
1	..	..	..	250	17	..	..	0	C	..	..	..	0	..
2	..	..	450	600	2,000	D	..	..	..	..	..	..	..	..
3	..	..	..	..	5	1	..	..	1	..	1,000	1,000, D	..	..
4	..	..	..	..	..	..	500	700	..	D	..	..	..	..
5	..	1,600	10,000, D	..	..	..	..	..	..	..	..	..	..	..
6	..	..	..	..	+	+, D	..	..	..	..	..	..	..	..
7	..	..	..	600	..	1,200	D	..	..	..	..	..	..	..
8	..	0	0	0	..	2	D	..	..	..	..	..	..	..
9	..	0	B	0	0	..	0	..	..	..	L	..	..	..
10	..	..	..	..	..	..	0	33	100, D	..	..	..	..	..
11	..	..	..	B	..	0	..	0	L	..	..	..	..	..
12	..	..	..	..	..	..	..	+	..	+	0	L	..	..
13	..	..	..	..	..	..	+	+	..	L	..	..	..	..
14	..	..	..	..	..	..	..	..	..	..	..	+	..	0, L
15	..	..	..	380	17,000	D	..	..	..	..	..	..	..	..
16	..	..	..	..	..	..	+	+, D	..	..	..	..	..	..
17	..	..	..	0	D, +	..	..	..	..	..	..	..	..	..
18	..	..	..	..	+, D	0	..	..	..	..	..	..	..	..
19	..	..	..	..	+	..	+, D	+	..	..	..	..	..	..
20	..	..	..	..	..	24	30	6	4	D	0	..	..	..
21	..	..	..	..	..	..	+	D	0	..	..	..	..	..
22	..	..	..	..	+	0	D	0	..	..	..	..	..	..
23	..	+	+	..	..	..	L	0	..	..	..	..	..	..
24	..	..	..	..	+	0	0	0, C	..	..	..	..	..	..
25	..	..	..	0	..	..	+	..	..	D	..	..	..	..
26	..	..	..	..	..	+	D	+	..	..	..	..	..	..
27	..	..	..	..	..	..	..	..	..	+	+	+, D	+	..
28	..	..	..	..	..	..	+	..	+, D	..	..	..	..	..
29	..	..	..	..	..	0	..	..	..	+, D	0	..	..	..
Type V														
1	..	..	..	16	200, D	..	..	..	..	..	..	..	..	..
2‡	..	..	..	..	..	..	3	5	0	S H	D	..	..	..
3	..	..	..	..	0	..	..	..	..	..	..	..	+	D
4	..	2	4	..	200	400	D, +	..	..	..	..	..	..	..
5	..	..	..	..	+	+, D	..	..	..	..	..	..	..	..
6	..	..	..	..	..	50	5	1,700§	0	0	..	L	..	..
7	..	..	+	..	..	+	D	+	..	..	..	..	..	..
8	..	..	..	..	..	..	..	+	..	..	+, D	0	..	..
9	..	..	..	..	..	..	0	D	+	..	..	..	..	..
10	..	..	..	..	+	..	..	0	C	..	..	..	..	..
11	..	..	..	..	0	..	..	+	D	..	..	..	..	..
12	..	..	..	..	+	+, D	+	..	..	..	..	..	..	..
13	..	..	..	+, D	+	..	..	..	..	..	..	..	..	..
14	..	..	..	..	..	..	..	..	+	D	+	..	..	..
15	..	..	..	+	..	..	..	0	L	..	..	..	..	..
16	..	..	..	..	..	+	+	L	..	..	..	..	..	..
17	..	..	..	+, D	+	..	..	..	..	..	..	..	..	..
18	..	..	..	..	+	+	..	D	..	..	..	..	..	..
19	..	..	0	..	0	..	D	+	..	..	..	..	..	..
20	..	..	..	..	..	..	..	+, D	+	..	..	..	..	..

* First day of serum treatment.
† Empyema (Str. haemolyticus) and otitis media (Staph. aureus also); recovered.
‡ Treated with type II antibodies.
§ Retained placenta removed on this day.
D indicates died; L, lysis; C, crisis; SA, Staph. aureus; SH, str. haemolyticus; +, pneumococci cultured from broth; no counts made, and B, pneumococci in broth culture; plates sterile. The numbers represent colonies per cubic centimeter of blood. Cultures that were made after death were made from heart blood at autopsy.

TABLE 14.—*Résumé of the Autopsy Observations in Cases of Pneumonia Due to Type II and Type V Pneumococci*

	Type II Pneumonia		Type V Pneumonia	
	Lobar Pneumonia	Broncho-pneumonia	Lobar Pneumonia	Broncho-pneumonia
Number of cases	38[a]	10	22[b]	20
Pulmonary involvement				
1 lobe	8	2	6	4
2 lobes	13	3	8	2
3 lobes	13	2	8[b]	3
4 lobes	3	0	0	0
5 lobes	1	3	0	11
Unilateral	24	3	20[b]	7
Bilateral	14	7	2	13
Purulent pneumococcic complications				
Empyema [c]	7[1]	2	7[2]	4[2]
Pericarditis	3	1	5	0
Vegetative endocarditis	5	1	1	0
Meningitis	3	1	0	0
Pulmonary abscesses [d]	8[5]	1	4[2]	4
Bronchitis	15	4	15	10
Tracheitis	6	3	8	4
Skin abscess [e]	3	1	0	3
Otitis media, mastoiditis	1	0	0	2
Peritonitis [f]	0	0	2	3
Slimy pneumonic exudate	4	0	0	0
Nonseptic complications				
Sterile pleural effusion [c] (100 cc. or more)	7[3]	2[1]	8[1]	3[3]
Fibrinous pleuritis [c f]	36[6]	4[1]	18[3]	13[3]
Atelectasis	2	0	2	4
Organization of lung	6	1	3	6
Infarcts, thromboses	4[g]	3[h]	3[i]	2[j]
Acute hepatic necrosis	5	2	1	1
Jaundice	3[k]	1	2	1
Acute cardiac dilatation [c u]	7[3]	3	4[1]	3
Ascites	2[k]	2[l]	0	2
Purpura	0	0	0	0
Acute tubular nephritis	1	0	0	0
Other complicating conditions (excluding degenerative diseases)				
Fibrous pleural adhesions (old) [c]	28[11]	3[2]	11[4]	12[5]
Chronic pulmonary disease	7[m]	3[n]	4[o]	6[p]
Chronic endocarditis	3	3	3	1[q]
Infection of urinary tract	6	1	5	1
Ulcers (gastro-intestinal)	2	0	0	1
Cirrhosis of liver	7	1	1	1
Miscellaneous	0	0	5[r]	1[s]
Bacteriologic data				
Heart blood: positive	21	3	13	8
negative	10	3	4	6
Str. haemolyticus	1	0	1	1
Mixed infections [t]	6	3	3	3

[a] The significance of the superior letters used in the columns is as follows: a indicates including 1 with lobar pneumonia (right) and bronchopneumonia (left); b, including 3 with lobar pneumonia (right) and bronchopneumonia (left); c, the number with this complication on both sides is indicated by the superior numbers (in 3 of the cases of unilateral empyema [type V] there was a contralateral sterile pleural effusion); d, number of cases of parenchymatous necrosis noted only microscopically is indicated by superior number; e, including decubitus ulcers; f, including empyema; g, lung, left ventricle, kidney and spleen 1; right auricle 1; kidney 1; spleen 1; h, lung, right ventricle and spleen 1; coronary artery 1; cerebral artery 1; i, splenic vein 1; coronary artery 1; pelvic veins 1; j, lung and iliac veins 1; lung 1; k, 2 with cirrhosis of liver; l, 1 with cirrhosis of liver; m, emphysema 3; bronchiectasis 2; chronic bronchitis 1; bronchiogenic carcinoma 1; m, emphysema 3; o, emphysema 3; bronchiectasis 1; p, bronchiogenic carcinoma 1; metastastic carcinoma (breast) 1; bronchiectasis 2; emphysema 2; q, congenital heart disease; r, chronic passive congestion 2; salpingitis 1; hypertensive heart disease 1; abdominal hernia, incarcerated 1; s, subarachnoid hemorrhages; t, see tables 3 and 4, and u, dilatation was left sided in 1 case of type II bronchopneumonia and in 1 case of type V lobar pneumonia; other unilateral dilatations were right sided.

BACTEREMIA

The incidence of bacteremia and the percentage of mortality among patients with type II and type V pneumonia are recorded in table 12. Pneumococci were cultured from the blood stream in about half the cases of each type. In the 73 fatal cases of type II pneumonia in which blood cultures were made, 57, or 78 per cent, of the patients were bacteremic, but only 26, or 27 per cent, of the 96 who recovered showed positive results of blood culture. Of the patients with type V pneumonia, 38, or 68 per cent, of those who died and 5, or 11 per cent, of the 47 who recovered showed positive results of blood culture. Thus, bacteremia was three or more times as frequent among the patients who died as among those who survived. The high incidence of bacteremia in cases of both types may have an important bearing on the high mortality in these cases.[25]

There is an increasing incidence of bacteremia with advancing age. This may be related to the natural immune processes which become less effective in older persons. The cases of bronchopneumonia in which blood cultures were made are so few that deductions cannot be drawn. The irregular mortality and incidence of bacteremia with respect to the different age groups is consistent with the secondary character of these atypical cases. This indicates that the primary disease or other factors combined with the factors of immunity [26] bring about the fatal outcome.

The course of bacteremia in patients from whom multiple blood cultures were made is shown in table 13. The effect of serum therapy on bacteremia is discussed elsewhere.[23] The largest number of colonies per cubic centimeter of blood cultured from patients who recovered were 1,700 from a patient with type V pneumonia, 250 from a patient who did not receive serum treatment and 362 from a patient with type II pneumonia who received serum treatment. Much larger numbers were encountered in fatal cases shortly before death. It should be noted that death may occur in cases of bacteremia even after pneumococci can no longer be cultured from the blood stream. Transient and recurrent bacteremia also was encountered in the fatal cases.

AUTOPSY OBSERVATIONS

Focal and Other Infections.—Autopsies were performed on 53 patients with type II infections and on 46 patients with type V pneumococcic infection. The protocols, which included histologic studies in each instance, were reviewed in every case. In 5 (9.4 per cent) of

25. Bullowa, J. G. M., and Wilcox, C.: Incidence of Bacteremia in the Pneumonias and Its Relation to Mortality, Arch. Int. Med. **55**:558 (April) 1935. Cecil and Plummer.[12b]

26. Sutliff, W. D., and Finland, M.: Antipneumococcic Immunity Reactions in Individuals of Different Ages, J. Exper. Med. **55**:837, 1932.

the patients with type II infection and in 4 (8.7 per cent) of those with type V infection, no pneumonia was found which could be attributed to the pneumococcus. Sepsis (pneumococci in the culture of the heart blood) without a demonstrable focus was present in 3 of the cases of nonpneumonic type II infection; the fourth patient had pneumococcic meningitis and sepsis, and the fifth had otitis media due to type II pneumococci and meningitis due to Staphylococcus aureus. In 2 cases of type V nonpneumonic infection pneumococci were cultured from purulent otitic or mastoid exudate, but beta hemolytic streptococci were cultured from material from the blood and lungs in both cases and from material from the meninges in 1 case. The other 2 patients had focal purulent complications of bronchiogenic carcinoma, the type V pneumococci being cultured along with other organisms, from an infected hydrothorax in one and from a bronchiectatic abscess in the other.

The data with regard to the cases of pneumonia are listed in table 14. Some of the features are briefly mentioned here.

Character and Extent of the Pulmonary Lesion.—Bronchopneumonia was noted more frequently at autopsy than clinically. The pulmonary lesion was atypical in 10, or 21 per cent, of the cases of type II infection and in 20, or 47 per cent, of the cases of type V infection. In addition, 1 of the patients with type II infection and 3 of the patients with type V infection had lobar pneumonia involving the entire right lung and diffuse bronchopneumonia of the left lung. The greater incidence of bronchopneumonia is attributable to the fact that, particularly in the cases of type II infection, either the pulmonary lesion or its pneumococcic etiology or both were often first recognized at the time of autopsy. Among the patients with lobar pneumonia, bilateral involvement was relatively more frequent in the type II infection than in the type V infection, but the lesions were confined to one lung in most of the cases of either type.

Purulent and Other Complications.—The relatively high incidence of empyema (26 per cent), pericarditis (12 per cent) and peritonitis (12 per cent) among the patients with type V pneumonia and of endocarditis (12.5 per cent) and meningitis (8 per cent) complicating type II pneumonia is worth noting. The cases of peritonitis (3 in males and 2 in females) were all in adults between 28 and 48 years old. It is also of interest, because of the possible bearing on the clinical diagnosis, to note the large proportion of cases of tracheobronchitis. In most instances the bronchitis involved, in addition to the consolidated regions, lobes in which the parenchyma was not affected. Slimy pneumonic exudate, usually considered characteristic of infection with type III

pneumococcus or with Friedländer's bacillus, was noted in 4 cases of lobar pneumonia due to type II pneumococci.

Among the pleural complications, fibrinous pleuritis and sterile effusions were the most frequent. The presence of old fibrous pleural adhesions in more than two thirds of all the cases is of interest in view of the recent interest in pneumothorax therapy.

Bacteriologic Observations.—In all but 9 of the cases autopsy was performed within twenty-four hours after death. Type II or type V pneumococci in pure culture were recovered from the lung and other foci in almost every case, even when the autopsy was performed as long as nine days post mortem. These organisms were recovered also from the blood in the majority of instances. In only 3 cases were other organisms (beta hemolytic streptococci) cultured from this source. The frequency with which other organisms were cultured from all sources at autopsy is noted in table 14, and their sources are listed in table 4.

COMMENT

The purpose of this presentation has been primarily descriptive. It is part of a study designed to evaluate the significance of different types of pneumococci, particularly those recently differentiated from the old group IV, with respect to the host which they invade and the disease which they produce. No effort has been made, however, to include all aspects of the symptomatology, the physical signs and the results of therapy. There is presented here a base line which may be used, on the one hand, to compare the diseases caused by these two types of pneumococci with those resulting from other bacterial agents and, on the other hand, to evaluate the results of various general or specific therapeutic agents in cases of pneumonia due to these types. It may serve also to give a comparison of the characteristics of the disease caused by the same organisms in different localities.

The greatest significance of the recognition of the etiologic agent in cases of pneumonia, as in cases of other infections, is with respect to specific therapy. From this point of view the importance of distinguishing type V from type II pneumococci has been pointed out elsewhere.[27] We have here compared the pathogenicity for man of these two types of pneumococci. With respect to their close association with pulmonary infection, these two types are closely similar. They are comparable, in this respect, with type I and stand out in contrast to the type III pneumococci.

Within the lungs type V pneumococci may be said to produce, in general, a similar but less typical pulmonary lesion than is usually caused by type II pneumococci. Type V pneumonia is more often

27. Cooper and others.[1b] Finland and Winkler.[8b]

secondary to a serious disease. In a larger proportion of cases type V pneumonia is atypical or is so-called bronchopneumonia; but the patients with type V bronchopneumonia exhibit a clinical picture more like that of typical lobar pneumonia than do the patients with type II bronchopneumonia. The gradation from the most typical to the most atypical pneumonia would be as follows: type II lobar pneumonia, type V lobar pneumonia, type V bronchopneumonia and, lastly, type II bronchopneumonia. With respect to the commonest of the other types, the clinical picture of type V infections seems to occupy a middle ground between type I and type II infections, on the one hand, and the more atypical type III and type VIII infections,[9a] on the other hand.

SUMMARY

Both type II and type V pneumococci were found to be associated with pneumonia with great regularity. In a small percentage of cases these organisms were isolated from lesions due to focal infection, or they were present in the sputum or nasopharynx without relation to disease. Various characteristics of the infections, particularly pneumonia, caused by these two types of pneumococci are recorded.

Like pneumonia due to type II pneumococci, the cases produced by type V pneumococci are usually lobar in character. Atypical pneumonia or bronchopneumonia, however, is far more frequent in the cases of type V infection. Lobar pneumonia due to type V pneumococci may be less characteristic than the condition due to type II pneumococci.

NONBACTERIAL THROMBOTIC ENDOCARDITIS

CLASSIFICATION AND GENERAL DESCRIPTION

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According to Libman,[1] endocarditis may be classified as rheumatic, syphilitic, acute bacterial, subacute bacterial and indeterminate. The indeterminate group includes a number of heterogeneous types characterized by nonbacterial, verrucous endocardial deposits, which cannot clearly be placed under the preceding headings. Certain forms in this indeterminate group, occurring toward the end of chronic diseases like carcinoma, leukemia or nephritis, were called terminal endocarditis. These corresponded to the cachectic endocarditis mentioned by Harbitz.[2] In 1923 Libman and Sacks[3] further segregated from the instances of the indeterminate group four cases in which the clinical and pathologic features were sufficiently uniform to constitute a definite syndrome. Because of the peculiar appearance of the gross endocardial lesions in this group of cases, the condition was termed "atypical verrucous endocarditis." In 1932 one of us (L. G.)[4] made a detailed study of the pathologic changes of the hearts of eleven patients with this disease. In the course of this study a number of instances of a type of indeterminate endocarditis were encountered in which the condition differed from the "atypical verrucous" form and which required further study and classification. These and certain additional cases in which the condition was similar form the basis of the present report.

From the Medical Services and the Laboratories of the Mount Sinai Hospital.

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1. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813-818 (March 24) 1923.

2. Harbitz, F.: Deutsche med. Wchnschr. **25**:121-124, 1899.

3. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701-737 (June) 1924.

4. Gross, Louis: The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, pp. 527-550.

NOSOLOGY

The early division of endocarditis into verrucous and ulcerative forms was discarded because of a lack of correlation with etiologic and clinical features. Current classifications are based in part on etiologic grounds but chiefly on groups of clinical features which apparently constitute definite homogeneous syndromes. In general, endocarditis may be divided into three major types, bacterial, nonbacterial and syphilitic (table 1). The last mentioned may be listed as a major type, even though it occurs infrequently, with the reservation that it is seldom, if ever, a primary endocarditis, since it generally produces only a commissural and basal valvulitis. In bacterial endocarditis, organisms are almost invariably found in the vegetations and in the circulating blood.[5] In contradistinction to this, bacteria are not found in significant numbers in the vegetations at necropsy in the nonbacterial types of

TABLE 1.—*Classification of Endocarditis to Show Position of Nonbacterial Thrombotic Endocarditis*

1. Bacterial endocarditis (bacteria cultivated consistently from the blood intra vitam and from the vegetations post mortem; also rare cases of tuberculous endocarditis)
   A. Acute bacterial endocarditis (pyogenic organisms)
   B. Subacute bacterial endocarditis (nonhemolytic streptococci, gonococci, influenza bacilli, etc.)
      1. With bacteremia
      2. In the bacteria-free stage
2. Nonbacterial endocarditis (may be due to bacteria or other infectious agents but thus far not proved
   A. Rheumatic endocarditis
   B. Indeterminate endocarditis
      1. Atypical verrucous endocarditis (Libman-Sacks)
      2. Nonbacterial thrombotic endocarditis (described and classified in this report; includes many of the conditions called terminal or cachectic endocarditis)
3. Syphilitic endocarditis

endocarditis, nor can organisms be cultured from the blood stream during life. It must be borne in mind, however, that this may be due to the inadequacy of the methods available, and in this sense the term nonbacterial is a misnomer, as newer methods may disclose a bacterial or other etiology in some of these cases.

The major type of nonbacterial endocarditis comprises two subtypes—rheumatic and indeterminate endocarditis. The true nature of these is as yet undetermined. However, the word "undetermined" should not be confused with the connotation implied by Libman's term "indeterminate." With him, we use the term to indicate that the true position of a given condition relative to other diseases is as yet unclear, or indeterminate, from the point of view of both clinical and pathologic diagnosis. From this definition it is obvious that rheumatic endocarditis does not properly belong to the indeterminate category, since this

5. In the rare cases of tuberculous endocarditis reported the clinical picture of bacterial endocarditis is not present (Dressler, W.: Zur Kenntnis der Tuberkulose der Herzklappen, Frankfurt. Ztschr. f. Path. **26**:401-405, 1921-1922).

disease has a definite clinical picture and certain distinctive histologic features (for example, the specific Aschoff body) which sharply distinguish it from other lesions. It is therefore listed as a separate subtype in the nonbacterial classification.

The remaining forms of nonbacterial endocarditis form a second subtype and constitute the indeterminate type of endocarditis. These include atypical verrucous endocarditis (Libman-Sacks) as well as other conditions which we shall classify and describe in this report as "nonbacterial thrombotic endocarditis." In spite of the fact that atypical verrucous endocarditis has certain clinical and pathologic features which seem to entitle it to separate classification as a subtype of nonbacterial endocarditis, as in the case of rheumatic endocarditis, Libman expressed the belief that knowledge of this disease is as yet so fragmentary and its relation to other conditions is so uncertain that it is better to continue to consider it a division under the indeterminate subtype.

There remain therefore in the indeterminate classification a number of forms which differ clinically and pathologically from those mentioned. These apparently do not represent a homogeneous syndrome like rheumatic or atypical verrucous endocarditis but comprise a variety of conditions. In all of these forms nonbacterial, nonreactive or mildly reactive thrombotic vegetations are present on the cardiac valves. In many cases the thrombotic deposits are secondarily engrafted on a damaged valve, the damage usually being due to a completely healed rheumatic lesion. Such healed rheumatic valvulitis belongs in type VI of our classification (inactive or healed rheumatic fever).[6] Thus, these conditions may be classified under two different categories—type VI rheumatic fever (inactive or healed), because of the underlying rheumatic process, and nonbacterial thrombotic endocarditis, because of the secondarily engrafted thrombotic process. This dual classification is strictly analogous to the occurrence of bacterial vegetations in subacute bacterial endocarditis on a rheumatic process.

In choosing a title for this subdivision we sought some feature which occurred in all cases. As was mentioned before, we found this to be the presence of nonbacterial thrombotic vegetations on the valves. We are therefore employing the term nonbacterial thrombotic endocarditis as a general descriptive heading, although we are well aware of the shortcomings of such a name. We have deliberately avoided the use of the term thrombo-endocarditis, which was originally employed by Ziegler.[7] It was his belief that in a large number of instances

6. Gross, Louis, and Friedberg, C. K.: Lesions of the Cardiac Valve Rings in Rheumatic Fever, Am. J. Path. **12**:469 (July) 1936.

7. Ziegler: Verhandl. d. deutsch. Kong. f. inn. Med. **7**:339-343, 1888.

vegetations occurred not as a result of inflammatory disease but as marantic thrombi similar to thrombi in blood vessels. More recently, when the term thrombo-endocarditis is employed, it refers to a general grouping which includes rheumatic endocarditis as well as the conditions under discussion. It seems, therefore, that to attempt to employ the term in its original sense would lead to confusion. The use of the term simple endocarditis as suggested by Königer,[8] or simple thrombo-endocarditis, contributes nothing to the descriptive value of the title.

Since the individual types of nonbacterial thrombotic endocarditis cannot be distinguished by the histologic appearance of the lesion, classification will be based on their association with some significant clinical or clinicopathologic condition (table 2). When a more definite

TABLE 2.—*Classification of Forty-Seven Cases of Nonbacterial Thrombotic Endocarditis*

1. Cases in which the condition was associated with thrombocytopenic purpura, etc.		3
2. Cases in which the condition was associated with peculiar arthritis and involvement of serous membranes (in one case with periarteritis nodosa)		4
3. Cases of cachectic and infectious disease associated with chronically deformed valves, usually rheumatic		32
Carcinomatosis	7	
Glomerulonephritis (in one case associated with periarteritis nodosa)	5	
Pulmonary emphysema and fibrosis	3	
Rheumatic cardiovalvular disease with congestive failure	2	
Uremia	2	
Lobar pneumonia	2	
Leukemia	2	
Pseudoleukemia	1	
Miliary tuberculosis	1	
Chronic osteomyelitis	1	
Purulent mediastinitis	1	
Subarachnoid hemorrhage	1	
Cirrhosis of the liver	1	
Fibrinopurulent peritonitis	3	
4. Cases of cachectic diseases with verrucae on relatively normal valves		5
Carcinomatosis	4	
Uremia	1	
5. Unclassified		3

etiology is discovered, these descriptions and designations may be amplified.

In discussing the cases of terminal endocarditis which we include as instances of nonbacterial thrombotic endocarditis, Libman [1] pointed out that this group required renewed investigation. It was in the light of that suggestion that this study was conducted. We shall describe the gross and microscopic appearance of the various types of valvular lesions encountered and shall segregate the clinical syndromes with which nonbacterial thrombotic endocarditis is associated. In this connection we have tried to ascertain whether this type of endocarditis occurs merely as an accidental finding in commonly encountered diseases or whether it is present as part of definite syndromes comparable to

8. Königer, H.: Arb. a. d. path. Inst. zu Leipzig **1**:1-162, 1903.

rheumatic or atypical verrucous endocarditis. Finally, we have endeavored to ascertain whether any particular factors throw light on the etiology or pathogenesis of the endocardial lesions.

MATERIAL AND METHODS

This study is based on patients who came to autopsy in the Mount Sinai Hospital in the twenty years preceding the time of writing. During this period the diagnosis of indeterminate, terminal or nonbacterial thrombotic endocarditis was made at necropsy in about one hundred and fifty cases. For various reasons the majority of autopsy reports could not be used. In many instances more detailed investigation led to a revision of the diagnosis, as it seemed probable or certain that the vegetations indicated active rheumatic or bacterial endocarditis. In an even larger number, while the evidence of rheumatic or of healed bacterial endocarditis was uncertain, such possibilities could not be excluded and the cases were omitted. We have limited ourselves, therefore, to the cases in which the verrucae were of recent origin, because in these the possibility of confusion with the healed stages of known forms of endocarditis is less likely. In many cases in which the valves showed knobs or nodules which were completely organized or hyalinized, we could not be certain whether such lesions were of inflammatory or of thrombotic origin or were the result of degeneration or tension. Such cases were not included. When we had limited our material in this manner, there remained forty-seven cases in which the condition fulfilled our criteria of nonbacterial thrombotic endocarditis. A study of these forty-seven cases forms the basis of this report.

The specimens were prepared as described previously in other publications,[4] and blocks were cut according to the standardized method of Gross, Antopol and Sacks.[9]

PATHOLOGIC CHANGES IN NONBACTERIAL THROMBOTIC ENDOCARDITIS

The following description presents the cardiac pathologic picture of nonbacterial thrombotic endocarditis in general. Special points will be considered in connection with the several subdivisions according to associated clinical diseases.

Valvular Lesions.—Macroscopic Features: The most striking and characteristic feature was the presence of valvular vegetations, which were occasionally of unusual appearance but were not specific in form, size or location. They were frequently larger than those associated

9. Gross, Louis; Antopol, W., and Sacks, B.: Standardized Procedure Suggested for Microscopic Studies on the Heart, with Observations on Rheumatic Hearts, Arch. Path. **10**:840-852 (Dec.) 1930.

with rheumatic endocarditis. They never involved the mural endocardium or the pockets of valves as do those associated with atypical verrucous endocarditis.

The most common type of verrucous lesions was the pyramidal ridge (Gross [4]). This lesion consisted of narrow discontinuous bands of yellowish, confluent deposits, superimposed on and firmly attached to a ridgelike thickening of the closure line of a generally thickened valve. It was found in more than half the cases, without special predilection for any particular type. Frequently irregular clusters or rows of discrete or confluent pinhead-sized grayish or yellow verrucae, occasionally

Fig. 1.—Nonbacterial thrombotic endocarditis of the right aortic cusp associated with purulent peritonitis. The verrucae resemble the type seen in rheumatic endocarditis.

friable, were superimposed on the ridgelike thickenings, giving a crownlike effect (fig. 1).

More distinctive and next in frequency were the conglomerate, or massive thrombotic, vegetations (figs. 2, 3 and 4). They were the size of a pea, sometimes larger, grayish-pink or tawny, of granular appearance and usually friable; sometimes they had the appearance of bacterial vegetations. A rather characteristic feature was the tendency to involve the commissures of the mitral valve or of the pulmonic and aortic cusps, more rarely the nodulus Arantii of the aortic valve (fig. 4). In a few cases the vegetations took the form of knobbed stalks or pendulous tabs (fig. 5).

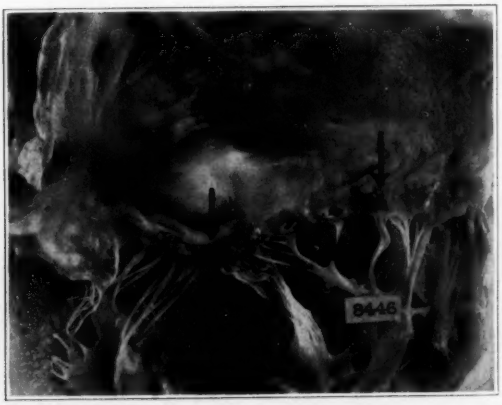

Fig. 2.—Nonbacterial thrombotic endocarditis of the mitral cusps associated with fibrinopurulent peritonitis. The lesion is of the massive conglomerate type.

Fig. 3.—Nonbacterial thrombotic endocarditis of the mitral cusps associated with carcinoma of the colon. The arrows point to massive conglomerate lesions, which have undergone considerable organization. Note the thickening of the valve leaflets and the chordae tendineae, evidences of a previous rheumatic infection.

Fig. 4.—Nonbacterial thrombotic endocarditis of the aortic cusps associated with carcinoma of the colon. Note the localization of the verrucae on the thickened corpora Arantii.

Fig. 5.—Nonbacterial thrombotic endocarditis associated with miliary tuberculosis. The arrow points to a lesion of the polypoid type. Note the fusion and thickening of the chordae tendineae, evidences of a former rheumatic infection.

The mitral valve showed thrombotic vegetations in all cases but one. The aortic valve was affected eleven times, the tricuspid valve five times and the pulmonic valve twice. There was little or no tendency for these vegetations to cause valvular deformities. Such deformities, when present, were obviously the result of old and inactive rheumatic endocarditis. In twenty-nine cases there was a significant thickening of the mitral valve, and in four or five cases there was thickening of the aortic and tricuspid valves. Mitral stenosis was present in nine cases, aortic stenosis twice and aortic insufficiency once. The nature of such

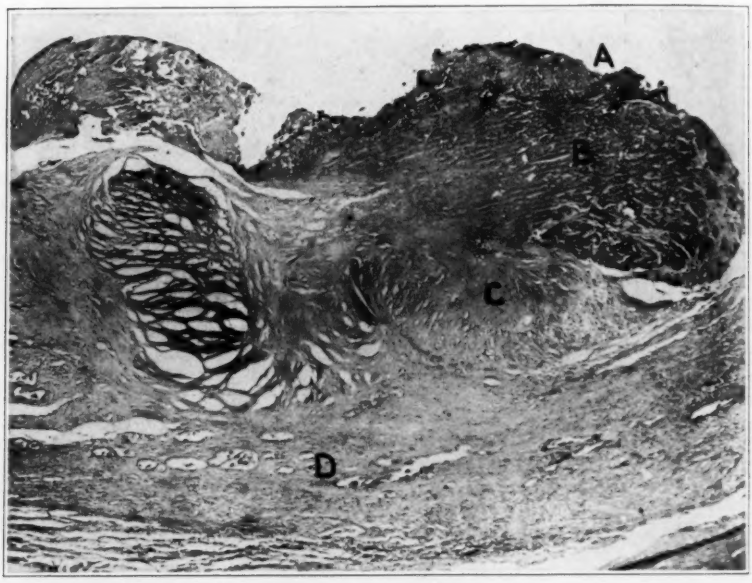

Fig. 6.—Nonbacterial thrombotic endocarditis of the mitral valve. Low power photomicrograph of a section stained with hematoxylin and eosin. *A*, a remnant of blood platelet thrombus superimposed on and fused with *B*, eosinophilic change of an organized valve lesion. *C*, hyalinization of an organized valve lesion. *D*, vascularization and thickening of an auricularis layer, probably evidence of old rheumatic infection. Note the mildness of the cellular reaction. No Aschoff bodies or acute auricular lesions are present.

disease and its relation to the pathogenesis of the verrucous lesions will be discussed later in this paper.

Microscopic Features: Microscopically, the vegetations consisted essentially of agglutinated blood platelet thrombi (fig. 6). In most instances there was already early evidence of organization, particularly

at the base and at the sides. The top of the thrombus was bare, but along the edges it was covered in part by an endothelial lining.

In eight cases the thrombotic material was superimposed on an irregular amorphous area of degeneration of the superficial portion of the valve substance, which we term eosinophilic change (fibrinoid) (figs. 6, 7 and 8). This material gave a peculiar brownish green appearance with Van Gieson's stain and stained deeply with eosin. Often the vegetations were composed almost completely of this degenerative material, which seemed to be the result of the primary change and on which blood platelets were secondarily deposited from the blood stream.

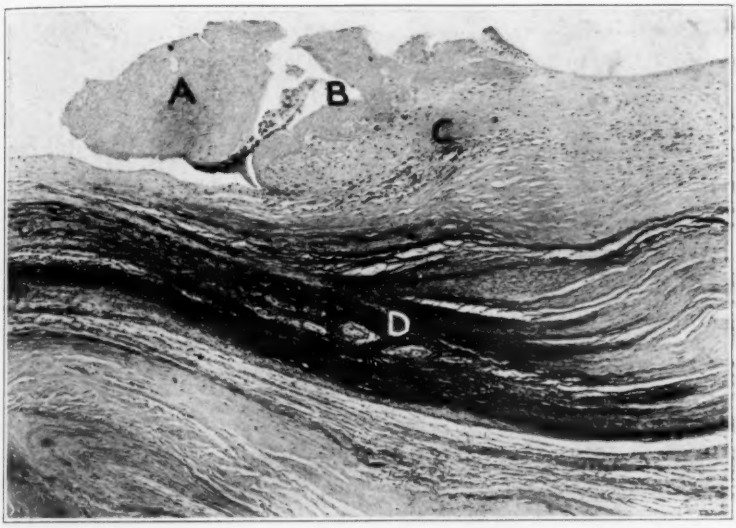

Fig. 7.—Nonbacterial thrombotic endocarditis of the mitral valve associated with rheumatic cardiovalvular disease. Low power photomicrograph of a section stained with Weigert's elastic tissue stain and Van Gieson's connective tissue stain. *A*, a recent blood platelet thrombus superimposed on and fused with *B*, eosinophilic change of an organized valve lesion. *C*, a mild cellular reaction. *D*, proliferation of the auricularis elastica, with considerable vascularization, probably evidences of a former rheumatic infection. No Aschoff bodies or acute auricular lesions are present.

The most remarkable feature of the histologic appearance of the valve was the absence or paucity of inflammatory reaction (figs. 6 and 7). Usually, there was a slight cellular proliferation, with rare capillaries limited to the base of the verruca where this was undergoing organization (fig. 6 and 7). In no instance were there any polymorpho-

nuclear leukocytes, and rarely were there lymphocytes or plasma cells. Most of the proliferating cells appeared to be of the fibroblastic and histiocytic variety.

In about two thirds of the cases the vegetation was deposited on a markedly thickened fibrotic cusp, showing broad, sometimes partially hyalinized collagenous bands. In twenty-one cases these valves showed the subendothelial fibro-elastic reduplication and distortion commonly present in rheumatic fever (fig. 8). In twenty cases the cusp was somewhat vascularized (figs. 6 and 7). This was true particularly in the instances of definite old valvular deformities (probably rheumatic).

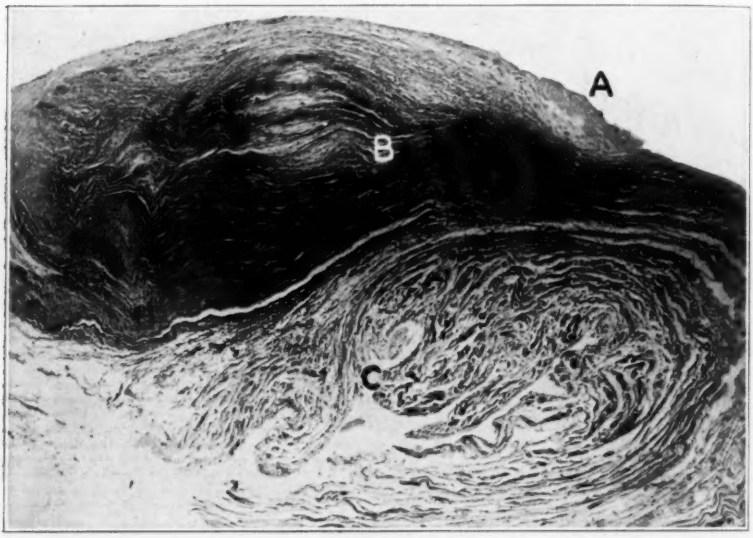

Fig. 8.—Nonbacterial thrombotic endocarditis of the mitral valve associated with carcinoma of the stomach. Low power photomicrograph of a section stained with Weigert's elastic tissue stain and Van Gieson's connective tissue stain. *A*, a remnant of vegetation deposited on the valve substance which has undergone eosinophilic change. Note the mildness of the cellular reaction. *B*, marked proliferation of the auricularis elastica, probably due to preceding rheumatic infection. *C*, chordae insertions. No Aschoff bodies or acute auricular lesions are present.

The slight degree of cellular proliferation and vascularization spoke for the inactivity of the rheumatic lesion.

Lesions of the Valve Ring.—The limited area of fibro-elastic tissue which joins the cusp of a valve to the adjacent cardiac structures has been termed the valve ring (Gross and Kugel [10]). Its essential impor-

10. Gross, Louis, and Kugel, M. A.: Am. J. Path. **7**:445-473, 1931.

tance lies in the fact that in rheumatic involvement of the valve the corresponding ring shows a fairly definite and characteristic inflammation. Among the cases of nonbacterial thrombotic endocarditis which we are discussing there was mild vascularization of the ring in thirty and slight infiltration with histiocytes, fibroblasts and occasional lymphocytes in fifteen. Involvement of the ring was confined almost entirely to the mitral valve. The lesions found were not those of active rheumatic fever but corresponded with changes in other parts of the heart indicating an old rheumatic infection.

Auricular and Ventricular Endocardium.—In no case did we observe typical macroscopic or microscopic lesions of the endocardium of the left auricle, such as are associated with recent or active rheumatic endocarditis. However, in forty of the forty-seven cases we found the microscopic lesions which Gross [11] described in cases of rheumatic cardiovalvular disease in which there were no clinical evidences of recent rheumatic infection and no Aschoff bodies or other histologic evidences of active disease. These lesions consisted essentially of distortions of the auricular endocardial elastica, the presence of subendothelial proliferation, termed reduplications, and of mild lymphocytic infiltration and vascularization of the endocardium and subendocardium.

Myocardial and Vascular Lesions.—The most striking vascular abnormalities occurred in the cases in which the condition was associated with thrombocytopenic purpura and with peculiar forms of involvement of the joints and of other serous membranes. Illustrations of these lesions appear elsewhere.[12] They consisted of proliferation, swelling and desquamation of the endothelium of the capillaries, arterioles and small arteries. Sometimes this proliferation led to localized verrucous or polypoid projections which encroached eccentrically on the lumen. More frequently the desquamated and degenerated cells formed granular plugs or hyaline thrombi, which partially or totally occluded the lumen. Occasionally endothelialized channels were visible in what had probably been organized granular or hyaline thrombi. Other vascular lesions corresponded to those described by Gross, Kugel and Epstein [13] as occurring in rheumatic fever, particularly in the peri-

11. Gross, Louis: Am. J. Path. **11**:711-735, 1935.

12. (*a*) Friedberg, C. K., and Gross, Louis: Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, Arch. Int. Med., this issue, p. 641. (*b*) Friedberg, C. K.; Gross, Louis, and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes, and Widespread Vascular Lesions, Arch. Int. Med., this issue, p. 662.

13. Gross, Louis; Kugel, M. A., and Epstein, E. Z.: Am. J. Path. **11**:253-279, 1935.

adventitial region of the aorta and the pulmonary artery (Gross).[14] The interstitial myocardial lesions of active rheumatic fever were absent, but in six cases there were scattered foci of interstitial myocarditis consisting of polymorphonuclear leukocytes or lymphocytes, with areas of destruction and scarring; in the instances in which there were marked vascular lesions extensive focal areas of degeneration and replacement fibrosis were present.

In summary, the condition in these cases was characterized pathologically by bland thrombi which were generally larger and often more friable than those characteristic of rheumatic fever. Unlike those in atypical verrucous endocarditis, these thrombi were limited entirely to the valves. The absence or paucity of recent inflammatory reaction in the cusps was characteristic. In these respects nonbacterial thrombotic endocarditis is to be differentiated from other forms of endocarditis. Finally, there was a marked tendency for this lesion to occur on scarred, thickened and deformed valves.

SUBDIVISIONS OF NONBACTERIAL THROMBOTIC ENDOCARDITIS

When possible, classification of the conditions in these cases was based on the clinical syndromes with which the endocarditis was associated (table 2). In some cases these associated clinical syndromes were commonly known disease entities, such as glomerulonephritis and leukemia. In seven cases, however, the associated clinical and pathologic manifestations presented unusual features requiring special study. Some of these are probably related to the conditions in the group of cases reported by Libman and Sacks,[3] Baehr, Klemperer and Schifrin,[15] Tremaine [16] and Christian.[17]

Nonbacterial Thrombotic Endocarditis with Thrombocytopenic Purpura.[12a]—The three patients were young women. Clinically, their symptoms were dominated by purpuric extravasations, epistaxes and other hemorrhagic manifestations. The classic features of essential purpura haemorrhagica were present. The septic course of the condition suggested a general infection, but cultures of the blood were sterile.

At necropsy there was bland thrombotic endocarditis of the mitral valve in all three cases and of the aortic valve as well in one of them. These valves showed verrucae of the conglomerate thrombotic type as well as the formation of ridges. Microscopically, there were no

14. Gross, Louis: Am. J. Path. **11**:631-645, 1935.

15. Baehr, G.; Klemperer, P., and Schifrin, A.: Tr. A. Am. Physicians **50**:139-155, 1935.

16. Tremaine, M. J.: New England J. Med. **211**:754-759, 1934.

17. Christian, H. A.: M. Clin. North America **18**:1023-1026, 1935.

Aschoff bodies or other lesions of acute rheumatic infection. The presence of an old rheumatic lesion was likely in one instance and was probable in the other two.

There were marked vascular lesions in the heart and in other organs of one of the patients. These consisted of hyaline and granular plugs in various stages of organization. The condition was interpreted as a general disease, probably infectious, with hemorrhagic manifestations due to a toxic effect both on the endothelium of the capillaries and on the bone marrow.

Nonbacterial Thrombotic Endocarditis with Arthritis, Inflammation of the Serous Membranes and Vascular Lesions.[12b]—This type, which was observed in four cases, also occurred in young women. There was a prolonged febrile course resembling a general infection, but numerous cultures of the blood were sterile. Polyarthritis, pericarditis, fibrinous pleurisy and pleurisy with effusion frequently dominated the picture. In two instances there was deforming arthritis, with fusiform joints. Ascites was recognized during life in one instance, and at necropsy there was subacute or subchronic polyserositis in all.

In addition to revealing the inflammation of serous membranes, necropsy showed rather characteristic grayish yellow friable vegetations of the conglomerate, or ridge, type on the mitral valve in each case, on the aortic valve in three and on the tricuspid and the pulmonic valve once each. There were vascular lesions resembling those described in the preceding group of cases. In one case there was, in addition, necrotizing panarteritis of the vessels of the myocardium, kidney, stomach and mesentery. The condition in this group was interpreted as a generalized infectious disease with marked affinity for endothelial structures.

Nonbacterial Thrombotic Endocarditis with Cachetic and Infectious Disease Associated with Chronic Cardiovalvular Disease.—There were thirty-two patients with a variety of clinical diseases. However, all of them showed in common an old inflammatory lesion of the valves. This old lesion was probably rheumatic in the great majority of cases, but in one the thrombotic lesion occurred on an aortic valve which was deformed by calcification (Mönckeberg [18] type). Although the verrucae themselves were recent, there were little or no valvular reaction, no Aschoff bodies and no acute pericarditis or acute auricular lesion. There was no history of rheumatic fever.

Five of the thirty-two patients presented diffuse glomerulonephritis. In three instances death occurred, with symptoms of failure of the right side of the heart apparently secondary to marked pulmonary emphysema and fibrosis with sclerosis of the pulmonary artery. In two other

18. Mönckeberg, J. G.: Virchows Arch. f. path. Anat. **176**:472-514, 1904.

patients with terminal symptoms of failure of the right side of the heart the primary cause seemed to be the valvular deformities themselves. In seven cases the essential clinical disease was carcinomatosis. There were apparently no symptoms directly referable to the endocardial lesions in these cases.

In general, we have found that when valvular verrucae are encountered in association with lobar pneumonia, they do not belong to the group of conditions which form the basis of this report. In the majority of instances such verrucae contain bacteria (that is, one is dealing with acute pneumococcic endocarditis) or the verrucae occur as part of an exacerbation of acute rheumatic endocarditis. However, in two instances there were fresh nonbacterial thrombotic vegetations occurring without simultaneous recent rheumatic disease and thus falling into the group under discussion. In each instance these occurred on definitely old rheumatic deformed valves.

There were ten additional patients with nonbacterial thrombotic vegetations superimposed on deformed rheumatic valves. The condition in these patients was associated with illnesses generally termed cachectic. In two cases the condition was uremia, due to malignant sclerosis and to arteriosclerotic contraction of the kidneys, respectively. There were two instances of acute leukemia and one of lymphadenosis, or pseudoleukemia. There was one instance of acute miliary tuberculosis following posttonsillectomy pulmonary suppuration. One patient had chronic osteomyelitis and fibrinopurulent peritonitis; one died of a subarachnoid hemorrhage, one of purulent mediastinitis and one of cirrhosis of the liver.

The remaining three patients showed nonbacterial vegetations superimposed on deformity of the valve not due to rheumatic infection. In one these vegetations involved the mitral, aortic and tricuspid valves, which were the seat of marked sclerosis; in another they occurred on an aortic valve deformed by syphilis, and in the third, on an aortic valve which was the seat of calcific sclerosis of the Mönckeberg type. All these three patients died of fibrinopurulent peritonitis.

Nonbacterial Thrombotic Endocarditis Occurring on Relatively Normal Valves.—The occurrence of so-called terminal endocarditis in instances of cachectic disease is well known. Yet compared to the frequency of occurrence of the cachectic diseases, the percentage of cases of such endocarditis is extremely small. Certain of these thrombotic vegetations are of obvious bacterial origin, resulting from a terminal or terminating antemortem bacterial invasion of the blood stream. In the series of cases which we have studied, nonbacterial vegetations when present were in almost all instances superimposed on valves

already damaged by preceding, usually rheumatic, disease. There remains, nevertheless, a group of cases in which the valves appeared to be normal and in which the occurrence of previous rheumatic disease could not be definitely established. It must be borne in mind that the line dividing normal from abnormal valves is not a sharp one. We have employed as our conception of normal valvular structure that given by Gross and Kugel.[10] Furthermore, we have been guided by other anatomic criteria for the presence of recent and healed rheumatic disease, such as the evidences of healed auricular,[11] ring,[19] vascular [13] and root lesions.[14] These have been published in detail elsewhere. A more rigid point of view or more minute histologic examination of serial sections of the valves in the cases under discussion might have revealed that rarely or never did thrombotic vegetations in these cases occur on normal valves. On the other hand, a broader interpretation of normality might have included a few additional cases under this heading. In any event, the essential observation that in the great majority of our cases vegetations occurred on abnormal valves would still be pertinent.

In five instances nonbacterial thrombotic deposits occurred on presumably normal valves. Four of the patients died of carcinomatosis, one of uremia. These cases did not differ clinically in any significant respect from those of carcinomatosis or uremia in the preceding group.

Unclassified Indeterminate Endocarditis.—There were three cases in which the condition could not be definitely allocated to any of the preceding types because the diagnosis clinically and after necropsy was obscure. One was an instance of severe anemia with hemorrhagic manifestations and high fever. The second was that of a woman of 42, who suffered from arthritis, pleural effusions, pneumonic symptoms, Raynaud's syndrome and fever. The third was that of a 21 year old girl, who had wild choreiform movements for three days, acquired hyperpyrexia (temperature 107 F.) and died four days after hospitalization (fig. 9). In all these cases there were nonbacterial vegetations on one or more of the valves.

Nonbacterial Thrombotic Endocarditis Associated with Periarteritis Nodosa (Polyarteritis).—Special mention should be made of the occurrence of periarteritis nodosa in two cases. Sacks [20] noted the association of periarteritis nodosa in several cases of indeterminate endocarditis. We have reported the association of periarteritis nodosa with active rheumatic heart disease.[21] One instance of nonbacterial

19. Gross, Louis, and Friedberg, Charles K.: Am. J. Path. **12**:469-493, 1936.

20. Sacks, B.: Personal communication to the authors.

21. Friedberg, C. K., and Gross, Louis: Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, with a Note on Abdominal Rheumatism, Arch. Int. Med. **54**:170-198 (Aug.) 1934.

thrombotic endocarditis associated with periarteritis nodosa fell into the subdivision associated with peculiar arthritis and involvement of the serous membranes. In the other case the condition was associated with glomerulonephritis and was placed in the subdivision of cases in which the condition was associated with cachectic and infectious diseases. It does not yet seem justifiable to group these cases in a separate subdivision, although further experience may indicate that this association of periarteritis nodosa and nonbacterial thrombotic endocarditis is no chance occurrence.

Fig. 9.—Verrucous indeterminate endocarditis of the unclassified subdivision associated with a condition resembling acute chorea. Low power photomicrograph of a section stained with hematoxylin and eosin. *A*, an overhanging thrombus of the mitral valve. *B*, active granulation tissue reaction, contrasting with preceding illustrations of nonbacterial thrombotic endocarditis. *C*, flat thrombotic deposits nearer the base of the mitral valve superimposed on *D*, palisade formation.

COMMENT

Brief comments as to the etiology and pathogenesis of the endocarditis found in these cases appear pertinent. The direct etiologic agent is unknown; neither is it known whether the identical agent is responsible for the various types of nonbacterial thrombotic endocarditis. In our series a previous rheumatic involvement of the valves had

occurred in more than three fourths of the cases. Whatever the immediate precipitating cause, such preceding valvular damage appears to be the most significant predisposing factor.

Despite their frequent association with an old rheumatic infection, we are at present inclined to believe that the verrucae were of rheumatic origin, because of these considerations: While the verrucae were obviously fresh, the manifestations of rheumatic disease were those of an old, healed infection. There were no acute inflammatory changes in the auricular endocardium, pericardium, myocardium or valve cusps. Despite careful examination no Aschoff bodies could be found. There was no clinical evidence of a recent rheumatic infection which would

Fig. 10.—Unusually large rheumatic verrucae, grossly resembling those seen in nonbacterial thrombotic endocarditis. Microscopically typical rheumatic valvulitis with Aschoff bodies in the myocardium. *A*, grossly visible vascularization. *B*, verrucae on the anterior mitral cusp.

correspond with the age of the fresh verrucae. Nevertheless, the possibility that these verrucae are atypical manifestations of a rheumatic infection cannot be eliminated. The large size of the verrucae does not exclude a rheumatic etiology, as we have recently seen large polypoid rheumatic verrucae over 0.5 cm. in diameter associated with typical rheumatic fever with Aschoff bodies in the myocardium (fig. 10).

It should be noted that the condition in many of the cases included here must be classified also as belonging to type VI in the classification of the rheumatic valvular lesions (inactive lesions without Aschoff bodies) presented by Gross and Friedberg.[6] The term nonbacterial

thrombotic endocarditis is merely a descriptive classification of the secondary thrombotic deposits occurring on valves showing inactive rheumatic valvular lesions (type VI). Similar nonbacterial thrombi may be secondarily deposited on syphilitic valves or on valves showing the alterations of atypical verrucous endocarditis or of Mönckeberg's sclerosis of the aortic valve or may occur as a primary change on apparently normal valves.

As far as we could determine, the verrucous endocarditis in these cases was not responsible for any clinical symptoms, nor was the course of the associated disease affected in any way. The association with many types of cachectic disease does not appear significant, because such endocarditis is decidedly infrequent in comparison with the tremendous number of necropsies on persons with such conditions as carcinoma, leukemia and uremia. We believe that the nonbacterial, nonrheumatic forms of verrucous endocarditis can occur as accidental insignificant complications of any fatal disease, especially when some previous disorder, usually rheumatic, has damaged the cardiac valves.

The conditions in the seven cases which constituted our first two groups showed certain clinical resemblances to atypical verrucous endocarditis which was described by Libman and Sacks [3] and to the cases of disseminated lupus erythematosus with extensive vascular lesions and a febrile clinical course which were reported on in detail by Baehr, Klemperer and Schifrin.[15] None of our patients, however, showed the characteristic cutaneous manifestations described by these writers. Similarities are seen in the frequent occurrence in their cases of involvement of the serous membrane, of purpuric manifestations and of vascular and endocardial alterations. There is some question as to whether the presence of disseminated lupus erythematosus is an essential difference. It is conceivable that instances of the condition belonging to the general group described by Baehr and his co-workers might occur without the striking cutaneous lesions but with the other associated clinical and histologic features of the disease. It should be added, however, that aside from the absence of lupus erythematosus in our cases, the manifestations in the joints were more marked and produced more conspicuous deformities than those that occurred only occasionally in the cases of Baehr and his co-workers, the involvement of serous membranes was more extensive and dominated the clinical picture, and the vascular lesions were not entirely identical. Furthermore, the purpuric manifestations and the hematologic findings were never as marked in Baehr's cases as in those of our first group, in which they formed the essential clinical features.

Recently Tremaine [16] reported two cases of "subacute Pick's disease (polyserositis) with polyarthritis and glomerulonephritis," and later Christian [17] mentioned these two cases as instances of "long-continued

fever with inflammatory changes in the serous and synovial membranes and eventual glomerulonephritis, a clinical syndrome of unknown etiology." The condition in these cases presents many resemblances both to that in the cases of Baehr, as Tremaine pointed out, and to that in our cases in which there was involvement of the serous membrane (group 2). The condition in one of Christian's cases showed the features of disseminated lupus erythematosus. No special mention was made of vascular lesions, although an indirect reference to them was contained in Tremaine's description of the kidney. Despite the undoubted similarities of the conditions in these various groups of cases, definition of their exact interrelationship must be reserved until more is known of their etiology or until definite, rigid criteria can be set up for a clinical pathologic syndrome. For the present it is essential to call attention to this important group of conditions, so that they may be recognized when encountered clinically and so that they may be studied for further clarification.

SUMMARY

A study was made of one hundred and fifty cases with autopsy in which the condition was diagnosed anatomically as indeterminate, terminal or thrombotic endocarditis. In forty-seven cases there was microscopic evidence of fresh thrombotic vegetation, with little or no recent valvular reaction, without bacteria and without associated clinical or pathologic evidence of recent rheumatic infection or of atypical verrucous endocarditis. The condition was termed nonbacterial thrombotic endocarditis. The remaining one hundred and three of the original one hundred and fifty cases considered were discarded because careful histologic examination revealed bacterial endocarditis, recurrent rheumatic infection or hyalinized fibrotic tabs due to tension and degeneration or representing healed lesions of known forms of endocarditis.

A classification of endocarditis is presented. The position of nonbacterial thrombotic endocarditis in this classification is discussed. The forty-seven cases presented in this report fall into five subdivisions. Two of these, comprising three and four cases, respectively, appeared to possess clinical and pathologic features in common. In the first, the thrombotic endocarditis was associated with thrombocytopenic purpura and in one instance with widespread vascular lesions. In the second, the endocarditis was combined with widespread inflammatory involvement of serous membranes, with polyarthritis, sometimes of peculiar form, and with a variety of vascular lesions. The third group comprised thirty-two cases in which the endocarditis occurred in the course of a number of cachectic and infectious diseases, including carcinomatosis, leukemia, uremia, peritonitis and pneumonia. The distinguishing feature of this group was the occurrence of the vegetations

on valves which had invariably been deformed by preceding disease, usually by rheumatic inflammation. In a fourth, smaller, group, comprising four instances of carcinomatosis and one of uremia, vegetations were present on presumably normal valves. The fifth group comprised three cases in which the condition could not be classified.

Nonbacterial thrombotic endocarditis is viewed as an accidental occurrence in the course of any fatal disease, without appreciable clinical significance. Its development is probably dependent on previous damage to the cardiac valves. In our cases such previous damage was almost invariably due to an old rheumatic infection. While it does not seem probable that the verrucae in themselves were of direct rheumatic origin, this possibility must be borne in mind. In the first two groups of cases mentioned, the endocarditis might have been dependent also on some toxic agent which appeared to have a special predilection for endothelialized structures.

NONBACTERIAL THROMBOTIC ENDOCARDITIS

ASSOCIATED WITH ACUTE THROMBOCYTOPENIC PURPURA

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In a previous description of nonbacterial thrombotic endocarditis we referred to two groups of cases which apparently had certain clinical and pathologic features in common.[1] The present report deals with one of these groups, which consisted of three cases of nonbacterial thrombotic endocarditis in which there was a clinical picture of thrombocytopenic purpura (fulminating in two cases), associated in one case with widespread vascular lesions. A later report will describe the second group of cases, characterized by prolonged fever, polyarthritis, inflammation of the serous membranes and vascular lesions.[2]

Purpuric manifestations are occasionally observed in other forms of endocarditis, particularly in bacterial endocarditis. In rheumatic fever purpura rarely occurs in a widespread, generalized form. In two of the four cases of atypical verrucous endocarditis described by Libman and Sacks [3] purpura was a significant symptom, and in one of them there was a reduction of the blood platelet count to 70,000 per cubic millimeter. In four of the eleven cases of the same disease described by one of us [4] the patients exhibited extensive purpuric symptoms, and two showed moderate thrombopenia. Recently, Baehr, Klemperer and Schifrin,[5] in a study of twenty-three cases of disseminated lupus

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1. Gross, Louis, and Friedberg, C. K.: Nonbacterial Thrombotic Endocarditis: Classification and General Description, Arch. Int. Med., this issue, p. 620.

2. Friedberg, C. K.; Gross, Louis, and Wallach, K.: Nonbacterial Thrombotic Endocarditis, Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, Arch. Int. Med., this issue, p. 662.

3. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701-737 (June) 1924.

4. Gross, Louis, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, pp. 527-550.

5. Baehr, G.; Klemperer, P., and Schifrin, A.: Tr. A. Am. Physicians **50**: 139-155, 1935.

erythematosus, noted the presence of widespread vascular lesions and endocarditis. There was a frequent tendency in these cases to thrombocytopenia and purpura.

In all these cases purpura was an incidental symptom largely overshadowed by other manifestations of the disease in question. The purpose of this report is to describe three cases of nonbacterial thrombotic endocarditis in which purpura and other hemorrhagic symptoms were the dominating clinical features of the disease. The blood studies were characteristic of purpura haemorrhagica. Certain features of the clinical course in two of the cases suggested that we had been dealing with a generalized, possibly infectious disease. The presence of widespread lesions of the vascular endothelium in one of the cases indicated the possibility that the hemorrhagic symptoms were the result not merely of a diminution of the blood platelet count but also of a toxic effect on the capillary endothelium. This case, together with three additional ones in which there were almost identical clinical and pathologic pictures, will be described in detail by Baehr, Klemperer and Schifrin.[6] In their report these authors link up the clinical data with the vascular lesions and discuss at length the pathogenesis of this syndrome.

REPORT OF CASES

Case 1.[7]—*History.*—B. W., a 9½ year old girl, was admitted to the hospital in the service of Dr. Béla Schick, on Aug. 30, 1927. She had been suffering from headaches, listlessness, pallor, loss of weight and dyspnea for six months. In the six weeks preceding hospitalization she had had three attacks of hematuria associated with vomiting. Each attack lasted for several days and cleared up spontaneously. Her physician had made a diagnosis of nephritis. During the second attack, four weeks prior to her admission to the hospital there were "red spots" on the eyelids and later also on other parts of the body. She had had occasional bleeding from the gums. In the last week before her admission to the hospital pallor had become marked, and the skin had been tinged with yellow. In the last two days the temperature had been between 101 and 102 F.

Examination.—The patient appeared chronically ill, mentally alert, well nourished, precociously developed, exceedingly pale and somewhat icteric. The temperature ranged from 101 to 104 F. The pulse rate was 140 and the respiratory rate 24 per minute. The blood pressure was 108 systolic and 58 diastolic. Over the flexor surfaces of the arms and over the trunk and extremities there were many bluish red purpuric spots ranging in size from that of a pinpoint to that of a pinhead. They did not blanch on pressure. The scleras were somewhat jaundiced and the conjunctivae pale. There was an ecchymotic spot on the conjunctiva of the left lower eyelid. In the fundus of the right eye just above the

6. Baehr, G.; Klemperer, P., and Schrifin, A.: Tr. A. Am. Physicians, to be published.

7. This case is described and discussed in considerable detail by Baehr, Klemperer and Schifrin.[6] For a fuller description of the vascular lesions see their report.

disk there was a yellow area of exudate. There were ecchymotic spots on the buccal mucous membranes. The lungs were clear. The heart showed a slight, soft systolic murmur, heard best at the apex. The liver was felt 1 fingerbreadth below the costal margin. The spleen was just palpable. There was costovertebral tenderness on the right side.

Provisional Diagnoses.—Various members of the staff offered the following diagnoses: a blood dyscrasia such as purpura haemorrhagica, hemolytic icterus or leukemia; subacute nephritis, and subacute bacterial endocarditis.

Laboratory Examinations.—The blood count showed: hemoglobin, 28 per cent; erythrocytes, 1,500,000; platelets, 25,000; leukocytes, 13,000; neutrophils, 81 per cent; eosinophils, 1 per cent; lymphocytes, 12 per cent, and monocytes, 6 per cent. The coagulation time was nine minutes, and the bleeding time, twenty-one minutes. The tourniquet test gave a positive result. There was no clot retraction in twenty-four hours. There were 20 per cent reticulated erythrocytes. The fragility of the erythrocytes was normal. The icteric index was 22. These studies were made by Dr. N. Rosenthal.

Roentgen examination of the nasal accessory sinuses revealed no abnormality. Roentgen examination of the abdomen showed no evidence of renal calculus, but the spleen appeared to be somewhat enlarged or situated low. Roentgen examination of the long bones showed no abnormality.

Electrocardiographic examination showed that the QRS complex was half inverted in lead III. The T wave was inverted in lead III, and the rate was 146 per minute.

The urine had a specific gravity of 1.020. It contained albumin (1 plus), a few granular casts and leukocytes and rare erythrocytes in centrifugated specimens. A twenty-four hour specimen of urine showed an increased amount of urobilin but no bile.

The direct van den Bergh test showed hemolysis. The indirect test showed a dilution of 1:25,000 (4 mg.).

Chemical analysis of the blood showed: urea nitrogen, 23 mg. per one hundred cubic centimeters; nonprotein nitrogen, 50 mg.; uric acid, 5.2 mg., and cholesterol, 124 mg. The Wassermann test of the blood was negative. Blood cultures on three occasions were sterile.

Course.—Because of the marked anemia, the child was given two transfusions of citrated blood, each of 500 cc. of whole blood, with an interval of two days. The hemoglobin content rose from 28 per cent to only 34 per cent, and two days later it fell rapidly to 25 per cent. There was an increase in the quantity of urobilin excreted in the urine from 12.6 to 35 mg. in twenty-four hours. The platelet count varied between 20,000 and 40,000 per cubic millimeter of blood. The erythrocyte count was less than 1,500,000 per cubic millimeter of blood. The temperature continued to range between 100 and 102.6 F. The child's general condition grew progressively worse. Ten days after her admission to the hospital the hemoglobin content had fallen to 18 per cent. Splenectomy was performed after the patient was given 250 cc. of citrated blood. Another transfusion was given during the operation. She died suddenly at the conclusion of the operation.

Postmortem Diagnosis.—The anatomic diagnosis was nonbacterial thrombotic endocarditis, hemorrhages in the skin, mucous membranes, pleura, peritoneum and renal pelvis, jaundice, anemia and multiple infarcts of the spleen and kidney.

Gross Postmortem Examination.—The body was that of a well developed, well nourished girl. There was a greenish yellow, waxy pallor to the skin. The

scleras were jaundiced. There were numerous petechiae and purplish spots on the upper and lower extremities and on the trunk. The largest ones measured about 1.5 cm. in diameter; the smallest were the size of a pinhead.

The heart was of normal size, weighing 210 Gm. (fig. 1). There were numerous small hemorrhagic foci beneath the pericardium. There was no pericarditis. The left auricle appeared normal. The anterior and most of the posterior mitral leaflet showed diffuse thickening with definite ridge formation on the line of closure. At about the middle of the anterior leaflet, and situated on the closure line, there was a large, oval thrombotic mass firmly attached to the valve by a broad base. The mass measured approximately 5 mm. in width and 1.5 cm. in length and was raised about 6 mm. above the level of the cusp. Immediately anterior and somewhat inferior to this vegetation there was a smaller pendulous

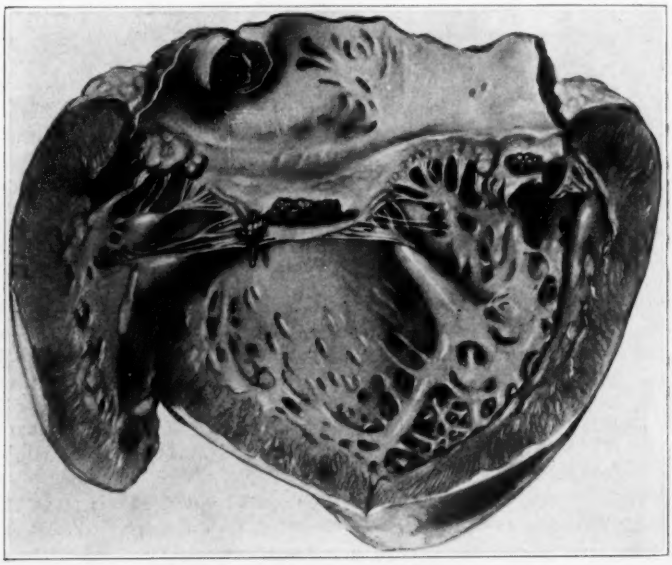

Fig. 1.—Nonbacterial thrombotic endocarditis (massive conglomerate type) of the mitral cusps.

growth attached by a narrow pedicle. On the closure line of the posterior leaflet there was a similar but smaller thrombotic mass somewhat larger than a split pea. The thrombotic material consisted of confluent granular, friable vegetations. The chordae tendineae showed slight thickening. The left ventricular musculature was hypertrophied. The aortic valves were normal. The right auricular chamber was somewhat dilated. A slight granular thickening was noted on the right cusp and a subendocardial hemorrhage above the insertion of the anterior cusp of the tricuspid valve. The right ventricle was slightly hypertrophied. The pulmonic cusp was normal.

The lungs showed subpleural hemorrhages. There was some cloudy swelling of the liver. Both kidneys showed several large, old infarcts.

The spleen, which was removed at operation, was about one and one-half times the normal size and contained two small yellowish infarcts extending to the periphery in cone shapes. An accessory spleen was present in the gastrosplenic omentum.

Microscopic Postmortem Examination.—Examination of the heart showed that there was no endocardial lesion in the left auricle. The ring of the posterior mitral valve contained a few round cells and capillaries. The cusp itself was slender. About midway along the cusp there were mushroom-shaped projections on the auricular surface external to the subendothelial elastica, consisting of proliferated cells, mostly histiocytes, fibroblasts and lymphocytes. In the center there was scarring. On either side endothelial proliferation was present. There was no

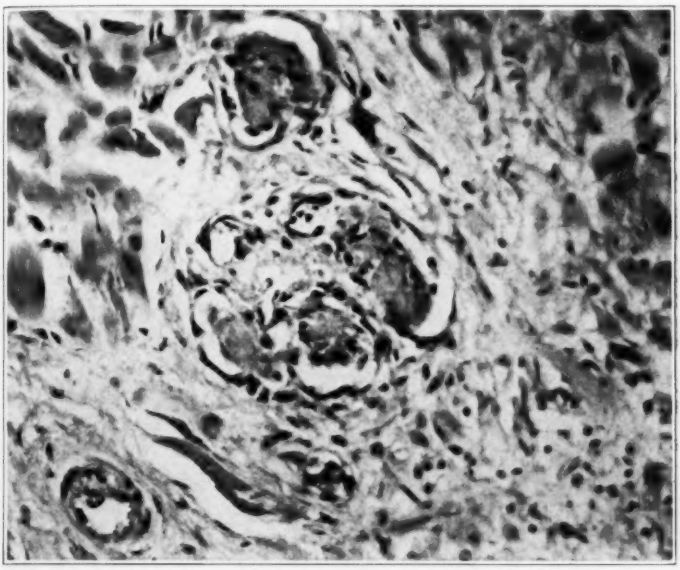

Fig. 2.—Myocardium of the left ventricle. Hematoxylin and eosin stain; high power. Note the vessel in the center with granular plugs and recanalization of the lumen.

reaction in the cusp. The anterior cusp of the mitral valve appeared normal except for the region of the closure line, where the auricular portion of the valve was thickened and the elastica was proliferated. The endothelial layer was necrotic and replaced by fibrinoid material. Superficial to this and apparently broken off from it was a large, pendulous thrombotic mass containing fibrin, blood platelets and a few leukocytes. At the sides of the base there was early organization. In the cusp itself practically no reactive inflammation was present. Slight scarring and a few capillaries were noted in the ring of the tricuspid valve. Otherwise the tricuspid and pulmonary valves were normal. The myocardium showed diffuse, small, irregular areas of destruction and replacement fibrosis. The vessels showed widespread abnormalities throughout. Many of the capillaries and smaller

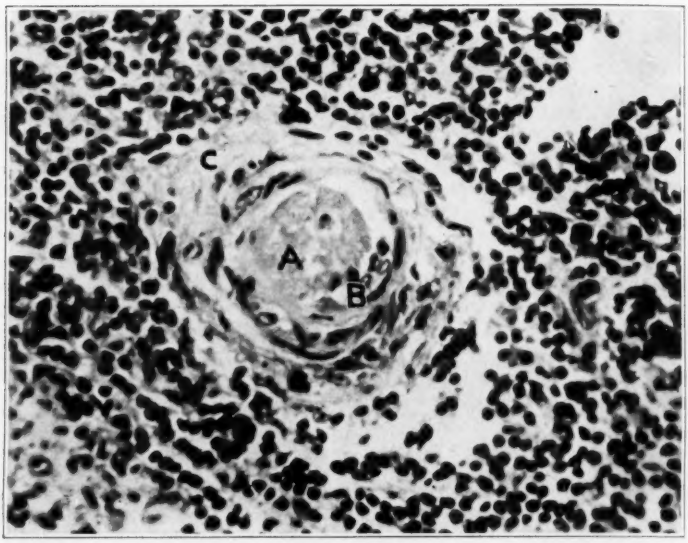

Fig. 3.—Splenic arteriole. Hematoxylin and eosin stain; high power. *A* indicates a granular thrombus plugging the lumen; *B*, endothelial proliferation (note the disorientation of the vessel layers), and *C*, adventitial edema.

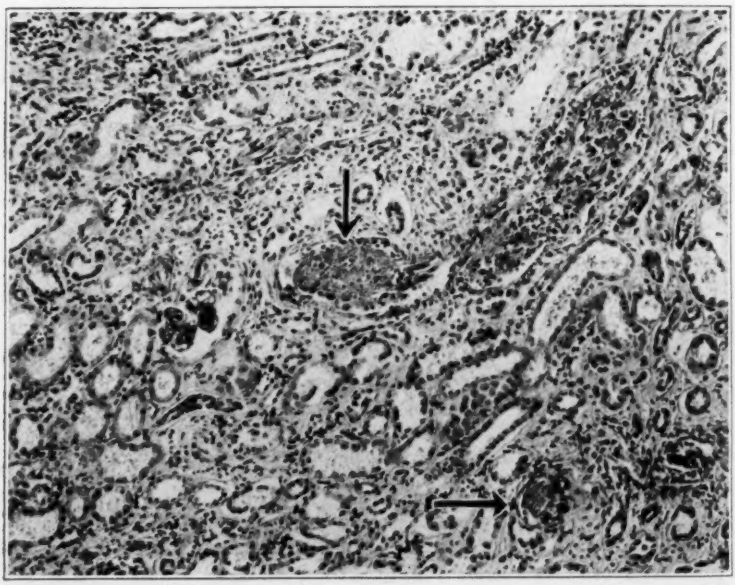

Fig. 4.—Renal arterioles with occluding granular plugs. Hematoxylin and eosin stain; low power.

arteries were partially or completely plugged by hyaline or granular degenerating masses. The endothelium was proliferated or desquamated, sometimes forming eccentric polypoid masses projecting into the lumen. Some of the capillary and arteriolar plugs showed recanalization (fig. 2).

In the lung there were edema and exfoliation of cells into the alveoli. Sections of the liver showed fatty and granular degeneration of the cells. The precapillary branches of the hepatic artery contained granular plugs, some of which were canalized. In the spleen there were multiple areas of necrosis about the malpighian corpuscles, and surrounding the areas of necrosis were zones of hemorrhagic reaction. The blood vessels were hyalinized and contained granular masses (fig. 3). The vessels of the kidney showed similar alterations. There were hyaline plugs in several of the larger arteries (fig. 4). Some of the glomeruli showed hyaline plugs in the tufts, varying from a small focus to the entire glomerulus. Some of the tubules contained hyaline cases. The capsule of the adrenal gland was thickened and congested. Many of the vessels in the cortex contained hyaline plugs.

Comment.—The symptoms in this case were essentially those of hemorrhagic disease. Because of the prolonged bleeding time (twenty-one minutes), the marked reduction in the number of platelets (25,000 per cubic millimeter), the presence of the Rumpel-Leede phenomenon and the absence of clot retraction, a diagnosis of purpura haemorrhagica seemed most likely. The septic course associated with continued fever, cardiac murmur, splenomegaly, hematuria and petechiae suggested the possibility of subacute bacterial endocarditis. Blood cultures were sterile on three different occasions.

Despite repeated transfusions and splenectomy, the patient did not recover. At necropsy there was widespread evidence of vascular disease characterized by the presence of hyaline and granular plugs in the capillaries and small arteries of the heart, liver, spleen, kidneys and adrenal glands and in some of the veins of the heart. In some instances the plugs were endothelialized, and new channels had formed in the lumens. The endothelium was desquamated or proliferated to form polypoid or verrucous masses which projected into the lumen and diminished its size. Baehr, Klemperer and Schifrin stated that they believed that the plugs were primarily platelet thrombi, which in later phases become organized by endothelial proliferation. Large friable verrucous lesions were situated on both cusps of the mitral valve. The vegetations were composed of a blood platelet thrombus which was undergoing early organization. Bacteria were absent. There was practically no reaction in the cusps. There were no Aschoff bodies or other evidences of acute rheumatism.

Case 2.—*History.*—E. K., a 21 year old milliner, was first admitted to the hospital, in the service of Dr. G. Baehr, on March 17, 1928. She had been treated in the outpatient department of the Mount Sinai Hospital for bleeding gums for one year and for nosebleeds for six weeks. Her past history included a nervous breakdown two years previously and simple enlargement of the thyroid gland

since puberty. She had had occasional nosebleeds (about three or four times each year) for the past ten years, the nosebleeds lasting generally for about one-half hour. In the preceding six weeks, however, these episodes had become more frequent and more severe, there having been eight nosebleeds in that interval which occurred spontaneously and lasted for about an hour. The gums had bled daily for the past year, but her dentist could find no local condition in the mouth to account for this. The patient said that black and blue spots had always developed after even slight injury. In addition, she had had clubbed fingers as long as she could remember.

Examination.—The patient appeared well developed, well nourished and not obviously ill. The size of the heart was normal, but there was a rough, prolonged, low-pitched systolic murmur following the first sound, heard best at the apex. The thyroid gland was symmetrically and moderately enlarged, and systolic and diastolic bruits were heard over it. There was incurvation of the finger-nails and a suggestion of clubbing. There were many purpuric and ecchymotic areas over both upper and lower extremities. The spleen was not palpable. The blood count showed: hemoglobin, 72 per cent (100 per cent equals 17 Gm.); erythrocytes, 5,100,000; leukocytes, 6,000; platelets, 168,000; neutrophils, 67 per cent; lymphocytes, 25 per cent, and mononuclears, 8 per cent. The tourniquet test showed a positive result. The bleeding time was two minutes, and the coagulation time, eleven minutes. There was slight clot retraction after two hours.

In the outpatient department three weeks earlier, the hemoglobin value had been 90 per cent; the platelet count, 80,000; the bleeding time, nine minutes, and the coagulation time, eighteen minutes. The urine showed a specific gravity of 1.022, albumin (1 plus) and occasional leukocytes.

Provisional Diagnosis.—A diagnosis of purpura haemorrhagica was made, but because of the association of slight fever, clubbing of the fingers and a cardiac murmur, a blood culture was made to verify the possible diagnosis of bacterial endocarditis. The culture was sterile. The Wassermann test was 4 plus on two occasions, and antisyphilitic therapy was started. There were no nosebleeds during the patient's stay in the hospital, and she was discharged with the diagnosis of chronic thrombocytopenic purpura.

History.—The patient was readmitted on April 24, 1933. In the interval she had had one or two nosebleeds monthly, usually just before or after the menses. She had suffered also from bleeding of the gums and had occasionally noted blood in the stools. The last menstrual period had lasted for two weeks. The immediate cause of hospitalization was severe epistaxis which had not been controlled after five hours.

Examination.—On this occasion the patient was pale, and both nostrils were filled with blood-soaked, oozing cotton. There was a small linear hemorrhage below the disk in the right fundus. There were multiple ecchymotic areas over the lower extremities and a few on the abdomen. The heart was enlarged to the right and left, and there was a blowing systolic murmur over the apex and to the left of the sternum. The blood pressure was 136 systolic and 80 diastolic. The liver was palpable 1 fingerbreadth below the costal margin and was slightly tender. The spleen was not palpable. The diagnosis was thrombocytopenic purpura.

The blood count showed: hemoglobin, 52 per cent; erythrocytes, 3,000,000; leukocytes, 7,400; neutrophils, 84 per cent; lymphocytes, 10 per cent; monocytes, 6 per cent; color index, 0.9, and platelets, 90,000. The coagulation time was four

minutes, and the bleeding time, forty-one minutes. Clot retraction was poor. The tourniquet test gave a positive result.

The urine contained a trace of albumin, many leukocytes and occasional erythrocytes. The Wassermann test of the blood was 4 plus; the Kahn test, negative. The urea nitrogen content of the blood was 13 mg. per hundred cubic centimeters. The blood pressure was 100 systolic and 74 diastolic. The pulse rate was between 100 and 110 per minute, and the temperature was between 100 and 103 F.

The nasal cavity was packed, snake venom was injected and transfusions and antisyphilitic drugs were given, without satisfactory control of the bleeding. On May 10, 1933, the splenic artery was doubly ligated, with the patient under spinal anesthesia, and a transfusion of 500 cc. of whole blood was given. Repeated examinations of the blood revealed that the platelet count was around 50,000 per cubic millimeter and that the hemoglobin content was about 50 per cent. There was an intermittent tendency to mild bleeding from the gums.

History.—The patient's third admission to the hospital was on Oct. 18, 1933. Death occurred within twenty-four hours. In the interval since her last discharge from the hospital she had felt well despite slight bleeding from the gums. The menstrual bleeding had been normal, and she had gained in weight and strength. There had been one nosebleed four weeks before her third admission to the hospital. This was easily controlled. Three weeks before her admission to the hospital she began to bruise with unusual ease, the nose and gums bled more frequently and profusely and she felt weak, dizzy and faint. Five days preceding hospitalization she began to menstruate, but the bleeding was abnormally profuse and persistent. She complained of headache, dizziness, weakness, nausea and sharp abdominal pain.

Examination.—The patient was acutely ill, febrile and pale. The pulse rate was 120 per minute. The blood pressure was 132 systolic and 76 diastolic. There were spongy, oozing gums, petechiae over the face, legs and flanks and large ecchymotic blotches over the thighs and forearms. The remainder of the observations were the same as those made previously. The hemoglobin content was 34 per cent, and there were 1,980,000 erythrocytes and 30,000 platelets per cubic millimeter of blood. The spinal fluid was normal. A transfusion of 500 cc. of whole blood (Unger method) was given, after which the temperature mounted rapidly to 105 F. The patient became comatose, and the extremities grew flaccid. She died from an intracranial hemorrhage the next day.

Postmortem Diagnosis.—The anatomic diagnosis was secondary anemia, nonbacterial thrombotic endocarditis of the mitral valve, hemorrhagic ascites, bilateral pleural hemorrhagic effusions, generalized ecchymoses of the skin and several mucosal surfaces, bilateral hemorrhagic cysts of the ovaries, subdural hematoma (right), pulmonary edema, perisplenic adhesions, acute infectious splenic tumor, vascular atrophy of the kidneys, parenchymatous degeneration of the viscera and persistent thymus.

Gross Postmortem Examination.—The body was that of a well developed, well nourished woman. There were purplish red petechiae and ecchymoses in the skin ranging from the size of a pinhead to that of a 5 cent piece, many of which were fading. On the inner aspect of the left thigh there was a large ecchymotic area with a purplish red border and fading center. There were a few hemorrhagic petechiae over both lower extremities and forearms.

The heart was somewhat enlarged and globular. The pericardium was normal except for a few circumscribed adhesions on the posterior aspect of the right auricle. There were several epicardial petechiae. The left auricle appeared normal.

The mitral valve was for the most part thin and translucent; but along most of the closure line of both cusps there were interrupted pyramidal ridges which were firm, brown and elevated about 7 mm. above the surface of the valve. One large ridge was situated along the middle of the anterior cusp, and two somewhat smaller ones, but of similar appearance, on the posterior cusp. These ridges appeared to be made up of, or capped by, fused flat irregular white nodules. There was no gross vascularization. The chordae tendineae were normal. The left ventricular cavity was slightly dilated, and its musculature was somewhat hypertrophied. The anterior papillary muscle was streaked with fat. The aortic valves were normal. The right auricular endocardium appeared normal. The tricuspid valves, the right ventricle and the pulmonary valves likewise showed no abnormality.

The lungs weighed 1,600 Gm. They were slightly edematous and contained petechiae and purpuric areas on the pleural surfaces. There were somewhat raised, circumscribed, oval reddish granular areas in the lower lobes. The liver weighed 1,650 Gm. and contained subcapsular hemorrhages. The spleen was markedly enlarged, weighing 300 Gm. It was soft and reddish brown, and its pulp scraped with ease. The follicles could not be distinguished. The splenic artery was obliterated. The kidneys were much smaller than normal, both together weighing 170 Gm. They were pale, yellow-red and flabby, with many subcapsular hemorrhages. There was some difficulty in stripping the capsule. The surface was irregular, finely granular and covered with hemorrhages. The cortex was narrow and irregular. The gastro-intestinal tract was normal except for subserosal and submucosal hemorrhages. There was a subdural hematoma in the right side of the brain.

Microscopic Postmortem Examination.—Examination of the heart showed that there was no acute lesion of the left auricular endocardium. There was a focal area of organizing lymphocytic pericarditis. The ring of the posterior mitral valve appeared normal. On the auricular surface of the cusp near the closure line there was a large hyalinized knob composed of broad masses of collagen fibers with few cells. The surface was capped by a thrombus of blood platelets. At the sides the nodule was covered with endothelium. Its base was organized and contained two small foci of lime. There was no cellular reaction or vascularization of the cusp, but the cusp was moderately thickened. At the tip there was increased proliferation of histiocytes. On the auricular surface and at the closure line of the anterior mitral cusp there was a large nodule similar to that on the posterior cusp. It was hyalinized and acellular. At the edges, however, there was slight cellular reaction. There was moderate histiocytic proliferation of the tip. The remainder of the cusp was normal. The aortic valve was normal. There were a few capillaries and round cells in the ring of the pulmonic cusp; otherwise it was normal. The tricuspid valve likewise was normal except for a few capillaries in the ring. In the myocardium there was occasional endothelial proliferation of the smaller vessels. There were irregular diffuse areas of scarring in the ventricular myocardium.

In the lungs there were large areas of hemorrhage, with edema and desquamated epithelial cells in the alveoli. There was severe autolysis of the renal parenchyma. The subcapsular glomeruli were hyalinized or fibrosed; the less superficial ones were well preserved. The small and medium-sized blood vessels were markedly narrowed and often entirely closed by endothelial proliferation, while the larger vessels were partially occluded by hyaline intimal thickening and elastic reduplication. The renal arteries of moderate size showed marked elastic reduplication.

The splenic pulp was crowded with red blood cells. There were also many polymorphonuclear leukocytes. A few megakaryocytes were seen. The smaller blood vessels showed marked intimal fibrosis and slight endothelial proliferation. The bone marrow from a vertebra showed activity, with many myeloid cells of all types. The liver showed moderate degeneration.

Comment.—This patient had been subject to bleeding from the gums, black and blue spots and severe nosebleeds for a long time and on three occasions had required hospitalization. The hemoglobin content originally was 90 per cent, but it had progressively diminished to 34 per cent, and the red cell count had decreased to 1,980,000 per cubic millimeter of blood. There were 80,000 platelets per cubic millimeter. The bleeding time was markedly prolonged, and there was poor clot retraction. The Rumpel-Leede phenomenon was present. While the diagnosis of purpura haemorrhagica appeared obvious, the association of fever, clubbed fingers and a rough prolonged systolic murmur at the apex of the heart again suggested subacute bacterial endocarditis. In this case the purpura was considered to be a toxic manifestation of that disease. This suggestion was not confirmed by repeated blood cultures, which were sterile. Various forms of therapy, including packing the nasal cavity, injecting snake venom and the repeated giving of transfusions, were ineffective. Ligation of the splenic artery gave a temporary remission, but the patient finally died apparently of intracranial hemorrhage.

At necropsy in addition to numerous hemorrhages there was a partially organized blood platelet thrombus on the mitral valve, with little inflammatory reaction in the cusp itself. The vascular lesions were slight in comparison with those in the previous case and were of dubious significance. The only marked lesions were in the kidneys, but these were interpreted as being secondary to pyelonephritis, although no renal symptoms were mentioned in the clinical history. The spleen was somewhat larger than it ordinarily is in a patient with idiopathic purpura haemorrhagica and showed acute hyperplastic and inflammatory changes (acute splenic tumor).

Case 3.—*History.*—M. S., a 30 year old saleswoman, was admitted to the hospital, in the service of Dr. E. Libman, on Jan. 14, 1923, complaining of a feeling of dulness for two days and anuria for one day. Five years previously she had had a "nervous breakdown." At that time she suffered from blueness and coldness of the hands and vague pains in the hands, fingers, back and knees. She was told that she had rheumatism. Shortly afterward she was confined to bed for about eight weeks with an attack of pleurisy. The vague pains in the extremities had persisted up to the day of her admission to the hospital. The tonsils were removed three months previously because of these pains. Following this operation the pains in the extremities became worse, and precordial pain was present for about ten days. For the past six months the gums had bled somewhat severely, even more markedly after tonsillectomy. Two weeks before her admission to the hospital she had a temperature of 102 F. for an entire week. Three days before she

entered the hospital her physician discovered a small hemorrhage in the conjunctiva of one eye. The next day she began to feel dull, drowsy, feverish and irritable. Her appetite had become poor, and coughing and expectoration were noted. For the past twenty-four hours she had been unable to urinate.

Examination.—The patient was an obese, acutely ill, toxic, pallid, mentally dull, dyspneic woman who coughed at intervals and raised small amounts of mucopurulent, slightly blood-tinged sputum. The temperature was 104.4 F., the pulse rate 138 and the respiratory rate 32 per minute. The blood pressure was 115 systolic and 60 diastolic. There was slight exophthalmos. The scleras were subicteric and the conjunctivae pale. There was a hemorrhage in the right fundus, the retinal veins were engorged and the arteries were tortuous. There was a small whitish area of exudate in the fundus of the left eye, and the disk margins were blurred on the right. The gums were bleeding. There were irregular ecchymotic areas and a small ulcer on the right side of the buccal mucosa, purpuric extravasations and small glistening lesions on an erythematous base on the hard palate. The sternum was tender. The lungs were dull to percussion over the lower three fourths of both sides posteriorly and over the lower half of both axillary regions. The breath sounds were diminished over these areas. There was feeble bronchial breathing, and bronchophony was noted at the angle of the left scapula. Subcrepitant râles were audible over the areas which were dull on percussion. The apex beat of the heart was seen and felt in the fifth interspace outside the nipple line. Percussion showed that the heart was enlarged to the left, extending 14.5 cm. in the fifth and 7 cm. in the second space from the midsternal line. There was a short, soft systolic murmur over the pulmonic area. The second pulmonic sound was accentuated and louder than the second aortic sound. The abdomen was slightly distended. The right kidney was palpable and somewhat tender. Over the dorsum of the left foot there were long, irregular, nonindurated, nontender purpuric extravasations. On the outer aspect of the right leg and on the pad of each thumb there were irregular nontender purpuric spots.

Provisional Diagnoses.—The diagnoses made included bilateral bronchopneumonia, toxic purpura, chronic nephritis (?) and sepsis (?).

Laboratory Examination.—The blood count showed: hemoglobin, 59 per cent (Kuttner, corrected); erythrocytes, 3,312,000; leukocytes, 13,800; platelets, 8,000; neutrophils, 94.6 per cent; lymphocytes, 3.3 per cent; monocytes, 0.6 per cent, and myelocytes, 1.3 per cent. The bleeding time was six minutes and the coagulation time eleven minutes. The tourniquet test showed a positive result. There was no clot retraction.

The Wassermann test of the blood was negative. Chemical analysis of the blood showed: urea nitrogen, 15.4 mg. per hundred cubic centimeters; incoagulable nitrogen, 37.6 mg.; uric acid, 5.4 mg., and creatinine, 1.4 mg. A blood culture was sterile. The urine had a specific gravity up to 1.025 and contained albumin (3 plus), occasional casts, many single leukocytes and a few erythrocytes. The phenolsulfonphthalein test showed 25 per cent recovered in two hours.

Course.—The patient's temperature ranged between 103 and 105 F. The pulse rate was between 120 and 160 and the respiratory rate between 30 and 60 per minute. She became progressively drowsier and then incontinent. The skin and scleras became icteric. There were fresh erythematous areas over both feet and purpura over the buccal mucosa on the left and over the sternum. On January 17 there was frank consolidation at the base of the left lung, and a pleural friction rub was heard over the precordium. The next day pulmonary edema was present. The patient vomited bloody fluid and died.

Postmortem Diagnosis.—The anatomic diagnosis was nonbacterial thrombotic endocarditis (mitral and aortic valves), acute fibrinous pericarditis, acute lobar pneumonia, jaundice and splenomegaly.

Gross Postmortem Examination.—The body was that of an obese, well developed woman. The scleras and skin were light yellow. Over the skin of the trunk and extremities there were a large number of purpuric spots varying in size and shape, the average diameter being 2 or 3 cm.

The heart was enlarged, weighing 600 Gm. There was shaggy pericarditis, especially on the posterior surface. The mitral valve was thickened. Along the line of closure of both cusps there was a golden yellowish, gelatinous, interrupted

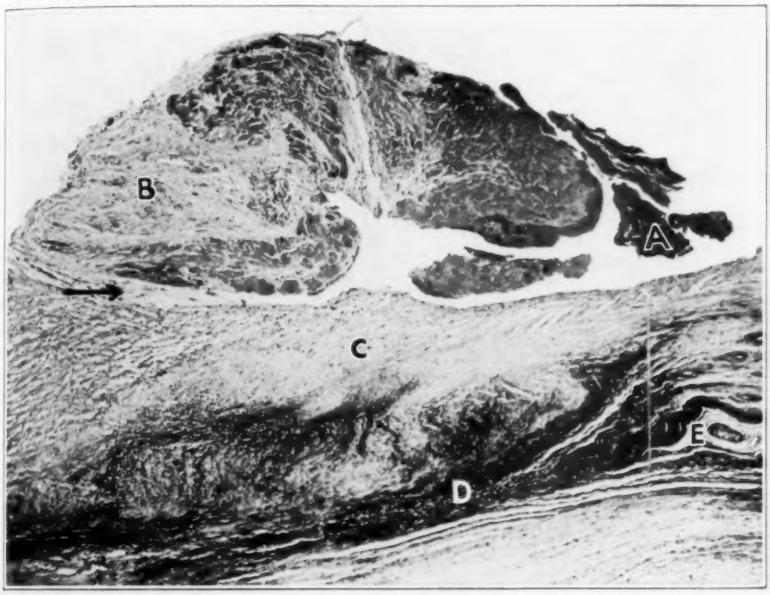

Fig. 5.—Nonbacterial thrombotic endocarditis of the posterior mitral cusp. Weigert's elastic tissue stain and Van Gieson's connective tissue stain; low power. A huge vegetation occupies the region above the arrow. *A*, indicates a blood platelet thrombus; *B*, an organized base of vegetation (note that the remainder of the vegetation is composed largely of swollen eosinophilic material); *C*, an auricularis layer (note the absence of inflammatory reaction); *D*, a marked increase of the auricularis elastica, and *E*, a muscular blood vessel (evidence of an old rheumatic process).

ridge of verrucae with an overhanging border and firm base, each portion of the ridge being about 1 cm. in length. On this ridge were a few translucent glistening granules the size of a pinhead. The chordae tendineae and their junctions with the valve were normal. The aortic valve showed on its posterior cusp a mound of heaped-up verrucae near the corpus Arantii. This consisted of numerous confluent, friable, grayish yellow deposits the size of a pinhead. In addition there was

a toothlike line of tiny verrucae on the right aortic cusp. The free edges of the valves were thin. The other valves were essentially normal. The lungs weighed 1,200 Gm. There were large areas of consolidation in the lower lobes of both lungs and in the upper lobe of the left lung. The abdomen contained a small amount of ascitic fluid. The liver weighed 1,800 Gm. Chronic passive congestion, cloudy swelling and diffuse jaundice were noted. The spleen was markedly enlarged, weighing 400 Gm. The malpighian bodies were enlarged, and the pulp was intensely congested, with an apparent cellular increase. The kidneys weighed 400 Gm. together. The capsules stripped with some difficulty, revealing a fairly granular surface. A cut section showed marked congestion and cloudy swelling.

Microscopic Examination.—The pericardium showed organizing pericarditis. There was a moderate amount of interfascicular fibrosis in the myocardium. No

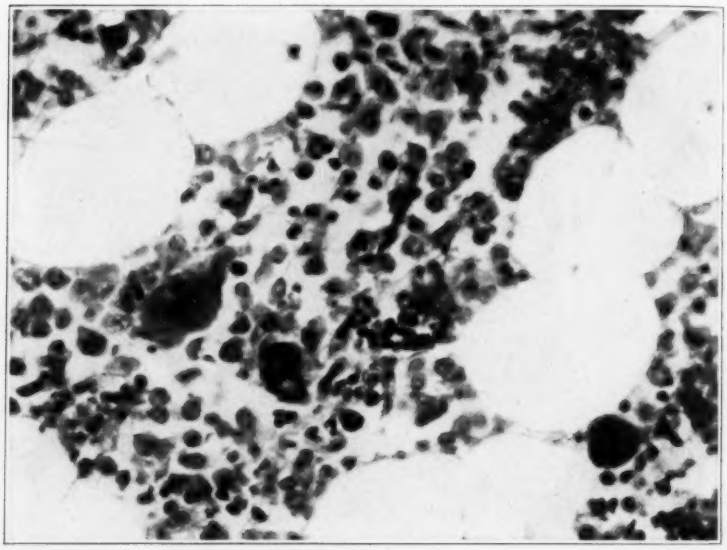

Fig. 6.—Bone marrow. Hematoxylin and eosin stain; high power. Note the normal cellular constituents, including megakaryocytes.

Aschoff bodies could be seen. There was no acute lesion of the auricular endocardium. The mitral valve was somewhat thickened. Fibrosis and vascularization of the ring were noted. At the base of the cusp there were several small arterioles with thick muscular coats. The cusp itself was moderately thickened, especially in the region of the closure line. This thickening affected chiefly the auricularis layer, which consisted of the broad bands of hyalinized connective tissue. The most superficial portion was capped by broad amorphous plaques of degenerated material, staining deeply with eosin and brownish green with Van Gieson's stain (fig. 5). Only a few ghosts of cells remained in this material, which we call eosinophilic swelling (fibrinoid change). There was seen slight cellular reaction, consisting only of a few lymphocytes at the base. At either side of the

vegetation there were thick-walled vessels within the substance of the cusp. In one section this eosinophilic material was covered by a broad, massive thrombotic deposit consisting of fibrin and blood platelets partly hyalinized and partly organized. The elastica of the mitral cusp was reduplicated and distorted beneath the region of the vegetation. The section of the posterior aortic cusp through the vegetation in the region of the corpus Arantii showed a thin cusp except at the level of the closure line. At that point the subendothelial fibro-elastic layer was markedly thickened and reduplicated. Superficially, there was a huge thrombotic deposit undergoing organization at the base, partly hyalinized and superficially capped by blood platelets. There was practically no cellular reaction, and only a few blood vessels were present at the base of the thrombus. Nearer the attachment of the cusp the subendothelial layer contained a row of somewhat thickened blood vessels. The right auricle showed a small area of inflammation containing blood vessels and lymphocytes. The tricuspid and pulmonic valves were essentially normal. In the region behind the pulmonary artery the vessels showed marked proliferation of the elastica and medial hypertrophy.

In the lungs were areas of lobar pneumonia and bronchopneumonia, as well as purulent bronchitis and extensive hemorrhages in the alevoli. There was focal nephrosclerosis. The liver showed moderate fatty infiltration. The sinuses of the spleen were dilated and congested. The bone marrow showed many megakaryocytes (fig. 6).

Comment.—This patient entered the hospital because of severe acute infection of the upper respiratory tract. Examination showed that there were widespread ecchymotic areas in the skin and mucous membrane of the mouth, icterus, high fever, signs of pneumonia, cardiac enlargement, an apical systolic murmur and accentuation of the second pulmonic sound. A diagnosis of bilateral bronchopneumonia was made. The purpura was considered to be a toxic manifestation of the disease. However, because the hemorrhagic symptoms were of six months' duration and because the blood showed the characteristics of purpura haemorrhagica, including a platelet count of 8,000 per cubic millimeter, that interpretation was discarded.

At necropsy organizing pericarditis and nonbacterial thrombotic endocarditis involving the mitral and aortic valves were present. There was no evidence that the recent verrucae were of rheumatic origin. There was, however, evidence of healed rheumatic infection in the mitral and aortic valves. In view of the evidence of previous rheumatic disease and the presence of organizing pericarditis, the occasional lesions in the heart were not considered to be of any special significance. The spleen was considerably enlarged, congested and soft.

COMMENT

After the observations on the reduction of the blood platelet count in certain forms of purpura by Hayem,[8] Denys[9] and others, these elements became the central point in the classification of purpuric disease.

8. Hayem, E.: Presse méd. **3**:233-235, 1895.
9. Denys, J.: Cellule **3**:445-461, 1887.

Two large groups were set up, the thrombocytopenic and the athrombocytopenic purpuras, depending on the presence of either a markedly diminished or a normal number of blood platelets. The former group includes idiopathic or essential purpura haemorrhagica or morbus maculosus Werlhofii, the blood in these cases showing, in addition to thrombopenia, an increased bleeding time, the Rumpel-Leede phenomenon and absence of clot retraction. The other group included the Henoch-Schönlein purpura, in which the blood picture is essentially normal. Further studies have indicated that such a dualistic grouping on the basis of the number of blood platelets is artificial without a clearcut differentiation on etiologic or pathogenic grounds. A considerable number of unrelated diseases, each with a distinctly different etiology, have now been observed in which there are hemorrhagic symptoms and a hematologic picture identical on the one hand with purpura haemorrhagica and on the other with Henoch-Schönlein's disease.

In the thrombocytopenic group it has become increasingly evident that so-called essential purpura haemorrhagica is not a specific clinical entity but rather a miscellany of heterogeneous diseases in which purpuric manifestations, a lower platelet count and other abnormalities of the blood constitute common incidental features. The scope of this diagnosis has become greatly narrowed by the recognition of the picture of purpura haemorrhagica in various leukemias, aplastic anemia and other blood dyscrasias, in a variety of intoxications, such as with benzene or arsphenamine, and in a number of infectious diseases, such as typhoid. That even the remainder of the conditions still left in this narrowed category of idiopathic thrombocytopenic purpura do not comprise a uniform entity is suggested among other things by the variable results of splenectomy, which in some instances effects a brilliant cure while in other cases of apparently the same disease it is totally ineffective. Furthermore, even in instances of cure following splenectomy, the mechanism of relief seems to differ in the various cases; in some this operation is followed by a restoration of the platelets to a normal number, and in others the amelioration of symptoms is effected without any alteration in the quantity of these elements. This suggests, at least, that the mechanism at fault is different in these two types of purpura.

In the cases which we have presented the condition bore all the characteristics of essential purpura haemorrhagica of the acute fatal variety. None of the known causes of symptomatic thrombocytopenic purpura were applicable in these cases. In each of the three cases the clinical impression was that of a general infection. In one case the presence of lobar pneumonia could account for the septic nature of the disease. In two cases a provisional diagnosis of subacute bacterial

endocarditis was made. One or more blood cultures were made in each case, but all cultures proved sterile. The course of the disease was rapidly downhill. Conservative measures were ineffectual. Transfusions hardly raised the hemoglobin or erythrocyte count at all, and the downward progress of the disease was not even temporarily stemmed. In the first two cases, despite repeated transfusions, the hemoglobin value dropped to 18 per cent and 30 per cent, respectively. Neither splenectomy nor double ligation of the splenic artery was of any avail.

The occurrence of icterus in two of the three cases was an unusual feature. In case 1 this appeared to be associated with a rapid destruction of the erythrocytes. The increased excretion of urobilin in the urine, especially after the transfusion, also points in that direction. One explanation for the icterus in these cases is the possible existence of hepatic damage, which has also been invoked as a partial explanation for the hemorrhagic symptoms in certain cases of purpura of toxic and infectious origin. In the three cases herein reported the liver was somewhat enlarged and showed cloudy swelling and granular and fatty degeneration. These alterations were hardly specific or severe enough to be significant, but the frequent meagerness of the anatomic changes even in cases of definite hepatic disturbance is well known. In the explanation of the jaundice in case 3 consideration must be given to the presence of a complicating lobar pneumonia, which has been associated with jaundice in 6.6 per cent of 635 cases in this hospital.[10] Its occurrence in such cases is not clear but has been ascribed to the decreased hepatic function in the presence of an increased formation of bilirubin.[11] But, as in the first case, in which pneumonia was not present, the icterus may have occurred as part of the general disease which produced the remaining symptoms.

Pathologically, there was nonbacterial thrombotic valvular endocarditis in all three cases, these having been selected from forty-seven cases of nonbacterial thrombotic endocarditis of various origins because of the association with thrombocytopenic purpura. In two of the three cases there was organizing pericarditis. The spleen was considerably enlarged in two cases and moderately enlarged in the third case. All the patients presented features usually associated with a general infectious disease. A detailed description of thrombotic endocarditis and a discussion of its classification and pathogenesis formed the basis of a previous report.[1] At present it will suffice to make a few brief comments regarding the thrombotic endocarditis in the cases under discussion. The vegetations did not belong to the bacterial group, which includes subacute bacterial endocarditis. There were no bacteria in the vegetations,

10. King, F.: Personal communication to the authors.
11. Rich, A. R.: Bull. Johns Hopkins Hosp. **47**:338-377, 1930.

no ulceration, no perforation of the valves or rupture of the chordae tendineae and no embolic glomerular lesions such as are generally present in subacute bacterial endocarditis. Grossly, the vegetations which were situated on the mitral or on the mitral and aortic valves did not have the characteristic warty appearance and, more particularly, were considerably larger than the vegetations usually observed in rheumatic fever. Microscopically, there were no interstitial valvulitis, no Aschoff bodies in the myocardium and no MacCallum lesions in the auricular endocardium. The vegetations consisted of a partially organized blood platelet thrombus with little or no reaction in the valve substance. In short, there was no evidence to suggest that the vegetations were part of an acute rheumatic endocarditis. In two cases there was moderate and in one case slight evidence of healed rheumatic infection. We have elsewhere indicated the frequency and importance of valvular damage due to such infection in predisposing to terminal nonbacterial thrombotic deposits.[1]

In addition to the various features mentioned, there were widespread unusual vascular lesions in one case, which consisted essentially of granular plugs in the capillaries and precapillary vessels. These plugs were undergoing organization and hyalinization. Their margins appeared endothelialized, and recanalization of the obstructed vessels occurred. As stated before, a detailed description and discussion of the pathogenesis of these lesions will be presented by Baehr, Klemperer and Schifrin[6] in the *Transactions of the Association of American Physicians* for 1936. In their report there is presented case 1 of this series together with three other cases of acute febrile anemia with thrombocytopenic purpura and diffuse blood platelet thrombosis of vessels. As in the latter three cases endocarditis was not evident, it appears that endocarditis is not an essential part of the disease. Furthermore, as these authors suggest, identical cases may occur without anatomically visible vascular lesions, the reduction in the blood platelet count being due not to intravascular thrombosis but to extravascular exudation through capillaries with damaged walls. Thus, the brother of one patient (case 1) died after apparently identical acute thrombocytopenic purpura, but no vascular lesions were discovered post mortem. Whether this explanation may be invoked for the last two cases in our series, in which there were no significant vascular lesions, or whether the lesions represented a considerably milder form of vascular injury it is impossible to state. However, it is of interest to note that our three cases are the only ones of eleven cases of thrombocytopenic purpura in which autopsy was performed in our hospital during the last thirteen years in which there was associated nonbacterial thrombotic endocarditis.

There is some question as to the primary importance of thrombocytopenia in these cases. Both the reduction in the blood platelet count and the hemorrhagic symptoms may have been manifestations of a general disease which injured the blood vessels and which also produced febrile anemia, thrombotic endocarditis, pericarditis and sometimes visible vascular abnormalities. Certainly the therapeutic failure of splenectomy and the abundance of megakaryocytes in the bone marrow preclude the usual type of purpura haemorrhagica resulting from the excessive splenic destruction of blood platelets or the inadequate formation of platelets in the bone marrow.

The primary importance of a reduction in the number of blood platelets in the causation of purpura has been especially stressed by Frank [12] and his followers. A good deal of evidence, however, has accumulated which casts doubt on the predominant significance of the reduction of these elements even in cases of thrombocytopenic purpura. That cure follows splenectomy even when a low platelet level persists after operation has already been mentioned (Kaznelson,[13] Ehrenberg,[14] Cori [15] and Kleeblatt [16]). While the favorable results following splenectomy have generally been ascribed to a diminished destruction of platelets, whether directly in the spleen (Kaznelson) or by removal of the toxic effect of the spleen on the bone marrow (Frank), Bedson [17] stated that he believed on experimental grounds that the effectiveness of splenectomy is due to the increase in the capillary resistance following this procedure. Failures of correlation between the diminution in the number of blood platelets and the hemorrhagic symptoms have been reported by Katsch,[18] Stahl,[19] Sternberg,[20] Gram,[21] Weil [22] and others. Experimental thrombopenia in animals has been produced without purpura and even without a prolonged bleeding time (Ledingham [23] and Roskam [24]). In their latest classification of hemorrhagic diseases,

12. Frank, E.: Neue deutsche Klin. **4**:395-437, 1930.
13. Kaznelson, P.: Deutsches Arch. f. klin. Med. **128**:119-130, 1918.
14. Ehrenberg, C.: Monatschr. f. Geburtsh. u. Gynäk. **51**:99-117, 1920.
15. Cori, G.: Ztschr. f. klin. Med. **94**:356-369, 1922.
16. Kleeblatt, F.: Beitr. z. klin. Chir. **120**:412-426, 1920.
17. Bedson, S. P.: J. Path. & Bact. **25**:94-104, 1922.
18. Katsch, G.: München. med. Wchnschr. **65**:897-900, 1918.
19. Stahl, R.: Deutsches Arch. f. klin. Med. **132**:53-68, 1920.
20. Sternberg, F.: Wien. Arch. f. inn. Med. **3**:433-452, 1922.
21. Gram, H. C.: On the Platelet Count and Bleeding Time in Diseases of the Blood, Arch. Int. Med. **25**:325-332 (March) 1920.
22. Weil, P. Emile: Rev. de méd., Paris **37**:81-102, 1920.
23. Ledingham, quoted by Morawitz, P.: Verhandl. d. deutsch. path. Gesellsch. **25**:32-45, 1930.
24. Roskam, J.: Sang **3**:497-528, 1929.

Pfaundler [25] and Naegeli [26] failed to divide them into the thrombocytopenic and the athrombocytopenic forms, and Morawitz [27] stated that hemorrhagic diatheses do not exist without vascular changes.

In anemia, leukemia, avitaminosis, sepsis and various infectious diseases hemorrhagic symptoms may occur with a thrombocytopenic blood picture. But similar purpuric manifestations occur in the identical diseases without any diminution in the platelet count. This suggests the possibility that in these diseases thrombopenia played no part or was only accessory to some other factor or factors in the causation of bleeding. This other factor may lie in the vascular damage which occurs in these diseases, as indicated by various anatomic studies.

In leukemia, in addition to the changes in the bone marrow, Naegeli has described infiltration and destruction of the vessel wall by leukemic infiltrations. In cases of meningococcemia histologic studies, especially by L. Pick,[28] have shown that the hemorrhages were due to bacterial emboli with direct destruction and inflammation of the wall of the vessel. In other infections with purpura M. B. Schmidt [29] sometimes noted irritative phenomena of the veins and capillaries, especially in the form of enlargement and proliferation of cells with nonbacterial granular thrombi. Herzog and Roscher [30] observed that in typhoid the hemorrhages were due to embolic involvement of the small vessels which were plugged with typhoid bacilli. In subacute bacterial endocarditis in which purpura may be present with or without thrombopenia, the hemorrhages may be due to emboli, to toxic arteritis (as described by Merklen and Wolf [31]) or to local closure by intimal proliferation. Reference has already been made to the four cases comprising a series which will form the basis of the report by Baehr, Klemperer and Schifrin,[6] in which these authors attribute the thrombopenia to vascular damage followed by intravascular thrombosis or extravascular exudation of blood platelets.

The condition in the cases here presented may be related to the larger group interpreted by Baehr [32] as the expression of a system disease affecting the capillaries and finer ramifications of the vascular tree and to the lupus erythematosus recently discussed by Baehr, Klemperer

25. Pfaundler, M., and von Seht, L.: Ztschr. f. Kinderh. **29**:225-380, 1919.

26. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931.

27. Morawitz, P.: Verhandl. d. deutsch. path. Gesellsch. **25**:10-32, 1930.

28. Pick, L.: Deutsche med. Wchnschr. **42**:994-998, 1916.

29. Schmidt, M. B.: Verhandl. d. deutsch. path. Gesellsch. **25**:10-32, 1930.

30. Herzog, F., and Roscher, A.: Virchows Arch. f. path. Anat. **233**:347-371, 1921.

31. Merklen, P., and Wolf, M.: Presse méd. **36**:97-100, 1928.

32. Baehr, George: Tr. A. Am. Physicians **46**:87-95, 1931.

and Schifrin.[5] This endotheliotoxic effect may in itself be adequate to explain the purpuric manifestations. The relationship of the reduced number of blood platelets to this generalized disease must remain hypothetic. In some cases, however, such thrombopenia may result from blood platelet thrombosis associated with vascular damage, as suggested by these authors.

SUMMARY

In a previous study on indeterminate forms of endocarditis, cases of nonbacterial thrombotic endocarditis were described and classified. In certain groups there were several clinical and pathologic features in common.

This report deals with one of these groups, comprising three cases, in which there were clinical features of acute fulminating (thrombocytopenic) purpura haemorrhagica.

Fever, purpura, epistaxis, bleeding of the gums, severe anemia, a low blood platelet count, poor clot retraction, a prolonged bleeding time and a rapid downward course were the dominant features. In each case observers considered the probability of a general infection, but blood cultures were sterile.

At necropsy, in addition to nonbacterial thrombotic endocarditis, each of the three patients showed an acute splenic tumor; in two cases there was organizing pericarditis and in one case widespread vascular lesions.

The possible relationship of an infectious process producing vascular damage and the purpuric phenomena are discussed.

NONBACTERIAL THROMBOTIC ENDOCARDITIS

ASSOCIATED WITH PROLONGED FEVER, ARTHRITIS, INFLAMMATION OF SEROUS MEMBRANES AND WIDESPREAD VASCULAR LESIONS

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In a previous report [1] several groups of cases were described and classified under the general designation of nonbacterial thrombotic endocarditis. This form of endocarditis is characterized by thrombotic vegetations, often of unusual size and appearance, with a minimum of reaction in the valve itself. It differs from the variety due to acute rheumatic infection and from the type described by Libman and Sacks as "atypical verrucous endocarditis."[2] Among the several subdivisions of nonbacterial thrombotic endocarditis, two appear to have certain clinical and pathologic features in common. One of these subdivisions (reported on elsewhere [3]) was represented by a group of three cases characterized by acute (thrombocytopenic) purpura haemorrhagica, nonbacterial thrombotic endocarditis and vascular lesions which were widespread in one case and considerably milder in the other two cases.

The present communication is a detailed account of another group of cases in which prolonged fever, arthritis, inflammation of the serous membranes and alterations of the blood vessels were prominent features. This group comprised four cases, all in young women. The onset was marked by acute polyarthritis simulating rheumatic fever. There was evidence of involvement of the pleura and pericardium with signs of fluid in these serous cavities. Clinical evidence of endocardial involvement was absent or minimal. There was persistent fever. Blood cultures were sterile. There were accompanying symptoms of nephritis without any evidence of renal insufficiency, except in a case in which

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1. Gross, Louis, and Friedberg, C. K.: Nonbacterial Thrombotic Endocarditis: Classification and General Description, Arch. Int. Med., this issue, p. 620.

2. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701-737 (June) 1924.

3. Friedberg, C. K., and Gross, Louis: Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, Arch. Int. Med., this issue, p. 641.

a moderate degree of renal insufficiency resulted from severe vascular lesions in the kidney. The course was subacute and progressive. Ascites developed toward the end and was discovered clinically or post mortem. Cardiac insufficiency was not a significant clinical feature. Death occurred as a result of cachexia or with symptoms of cerebral or pulmonary involvement. The arthritis differed in some respects from that in rheumatic fever and went on to marked deformity in two of the four cases. Postmortem examination revealed primarily subacute polyserositis, nonbacterial thrombotic endocarditis and vascular lesions of varying degrees of severity.

REPORT OF CASES

CASE 1.—I. G., a 24 year old West Indian Negress, was first admitted to the Mount Sinai Hospital on Feb. 5, 1929, where she remained until April 23, 1930. She was in the City Hospital from May 26, 1930, until May 11, 1931, and in the Mount Sinai Hospital again from Sept. 2, 1931, until Jan. 21, 1932, in the service of Dr. B. S. Oppenheimer.

History.—When this patient was first admitted to the Mount Sinai Hospital she complained of painful swollen joints, fever and sore throat for one month. Her family history did not include tuberculosis or rheumatic fever. Her past history was irrelevant; she had not suffered from rheumatic fever, sore throat, chorea, arthritis or scarlet fever. For the past year there had been various symptoms, but these had not been severe enough to interfere with her work. She had lost 15 pounds (6.8 Kg.) and had night sweats, occasional palpitation on exertion and a poor appetite. About a month preceding her admission to the hospital pain, swelling and redness developed in the right elbow, then in the left elbow and then in the wrists and ankles, the pains in one joint subsiding with the involvement of the next joint. Associated with these symptoms were a temperature as high as 102 F., sweating and a sense of chilliness. For two weeks the throat had been sore. She had been confined to bed for one month.

Examination.—The patient was acutely ill. The teeth were carious. There were enlarged submental and anterior cervical lymph nodes. The apical impulse was in the fifth interspace well within the left mammary line. There was a short, soft, blowing systolic murmur localized in the apical region. The second pulmonic sound was louder than the second aortic sound. The abdomen was essentially normal. There were tender swellings involving the interphalangeal joints of the ring and index fingers of the right hand. The right wrist was tender and painful on motion. There was some swelling of both knees and difficulty in extending them. The right ankle also was tender. On the dorsa of both hands there were soft, fluctuant swellings about the size of a walnut. These were probably due to the accumulation of synovial fluid. Vaginal examination revealed only profuse leukorrhea. The temperature at the time of the patient's admission was 103.2 F. The pulse rate was between 110 and 120 per minute. The blood pressure was 96 systolic and 50 diastolic. The blood count showed 70 per cent hemoglobin, 10,200 leukocytes, 80 per cent polymorphonuclears, 12 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. Urethral and cervical smears did not show gonococci. The sedimentation time was nineteen minutes.

A tentative diagnosis of acute rheumatic fever or acute infectious arthritis was made.

Course.—For sixty-two weeks the patient was almost continuously febrile. The temperature was generally between 100 and 103 F., occasionally reaching 104 F. Several times there was an afebrile interval of about a week. There were frequent recurrences of migrating arthritis, with redness, heat and swelling of the larger joints of both upper and lower extremities as well as of the interphalangeal joints. Occasionally there was a correlation between the involvement of a new joint and the sudden elevation of temperature. By the ninth month of illness persistent deformities had developed, consisting of spindle-shaped swellings of the joints of the fingers of both hands (fig. 1).

Despite a variety of abnormalities of the heart, there was never any certainty as to the presence of a valvular lesion. Throughout the period considered, there was always a short systolic murmur limited to the apex of the heart, and the second pulmonic sound was accentuated. One observer described a presystolic murmur, and another believed there was organic mitral disease, because of a short murmur he heard late in diastole. These signs were not confirmed by most of the other observers. In the third week there were definite pericardial and pleural rubs. In the fourth week there was clinical and roentgen evidence of pericardial

Fig. 1.—Proliferative arthritis of the joints of the hands of a patient with prolonged fever, inflammation of the serous membranes, vascular lesions and nonbacterial thrombotic endocarditis. Note the spindle-shaped joints of the right hand and the deformities with ankylosis of the joints of the left hand.

effusion. Repeated electrocardiographic examinations revealed the following: slight left axis deviation, notching of the Q R S complexes, changes in the RT transitions in the second and third leads, a broad and notched P wave in leads I and II, and inversion and coving of T_1 and T_2. The PR interval was 0.2 second. The changes were interpreted at various examinations as indicating myocardial damage, a poorly functioning myocardium or recent coronary occlusion. A roentgenogram of the heart was suggestive only of mitralization.

Shortly after admission to the hospital the patient showed pulmonary signs which persisted throughout her hospital stay. At first dulness and diminished bronchovesicular breathing were noted at the bases of both lungs posteriorly. On roentgen examination small pleural effusions were found at the bases. Repeated pleural taps yielded only 30 cc. of fluid containing 1,600 cells per cubic millimeter, almost entirely lymphocytes. These signs persisted, and in addition there were many medium moist râles over the same region. Repeated roentgen examinations were interpreted as showing the presence of unresolved pneumonia. There was only a slight cough and little sputum, which did not show tubercle bacilli or other

significant bacteria. Nevertheless tuberculosis was considered as a possible diagnosis.

Wassermann tests were all reported as 4 plus. Treatment with arsphenamine, iodides and bismuth did not alter the result. There was no clinical evidence of syphilis except generalized adenopathy, which was more marked for one week after the patient had been in the hospital for two months.

The urine at the time of the patient's admission to the hospital was normal, but in the ninth month of illness albuminuria developed, and there were many casts and red blood cells present. The blood urea content and various tests made of renal function were normal. During this period transient pretibial edema and some puffiness of the face were noted. The blood pressure was never elevated. The fundi were always normal. Roentgenograms of the various joints showed swelling of the soft parts and some atrophy. The white blood cell count was variable, sometimes rising to 30,000, with 90 per cent polymorphonuclears. On the other hand, there were occasions when, despite a high temperature and pulmonary involvement, there was no leukocytosis. The hemoglobin value gradually dropped to 55 per cent. Six cultures of the blood, aerobic and anaerobic, showed negative results. Similar cultures of the pleural fluid were likewise sterile. Various agglutination tests of the blood and cultures of urine as well as inoculation of guinea-pigs with the urine gave negative results.

At the conclusion of more than a year's continuous observation the patient left the ward of the hospital still febrile, the symptoms unchanged, to be observed further in the medical outpatient department. It was remarkable that despite the high temperature, the patient was fairly comfortable, except for recurrent articular pains. The clinical condition was considered as undiagnosed, although there were several possibilities under consideration.

During the time of observation in the outpatient department the patient showed symptoms and objective signs, but she refused to return to the hospital ward. In May 1930 she was admitted to the City Hospital, Welfare Island, where she was observed for one year, without any significant change in the clinical course. She was finally discharged, still febrile, the condition undiagnosed. She was again observed in the outpatient department, and she continued to have fever and suffered attacks of dyspnea and precordial pain. After a severe attack of dyspnea and precordial pain she was induced to reenter the hospital on Sept. 2, 1931.

Since her previous discharge the patient had lost 17 pounds (7.7 Kg.) in weight and had become exceedingly weak, so that she was incapable of any work. Frequently, especially after eating, she would experience epigastric distress and precordial pain, accompanied with dyspnea, orthopnea and palpitation, lasting for a few minutes. She frequently felt as though she were dying during these attacks. She still suffered generalized pains in "all her bones" and in many of the joints, all of which had become stiff. The joints of the hands were deformed.

On examination she appeared chronically ill, emaciated, weak and orthopneic. The eyelids were puffy. There was a perforation of the septum of the nose. Submaxillary adenopathy was present. The lungs revealed dulness at both bases, with diminution of the breath sounds and many medium moist râles on inspiration. The heart was enlarged both to the right and to the left, the apex being in the sixth interspace in the anterior axillary line. There were no murmurs. There was a presystolic gallop rhythm, especially marked in the third interspace to the left of the sternum. The blood pressure was 130 systolic and 80 diastolic. The abdomen was distended but otherwise was normal. The hands showed atrophy of the dorsa, with retraction of the intermetatarsal spaces and flexion contracture of the fingers. The fingers could not be extended beyond an angle of 120 degrees.

Thickening and deformity of the interphalangeal joints were marked. Besides the presence of syphilis the patient was considered most likely to have chronic rheumatic fever with chronic rheumatic myocarditis and chronic pneumonitis or an unusual form of infectious arthritis with arthritis deformans.

The blood count showed 66 per cent hemoglobin, 4,850,000 red blood cells, 10,000 leukocytes and 84 per cent polymorphonuclears. The urine showed albumin, red and white blood cells and casts, but tests of function showed no evidence of renal impairment. Roentgenograms of the joints showed atrophy of the bones and narrowing of the spaces, with areas of erosion. Roentgenograms of the ribs showed erosion of the fifth, sixth and seventh ribs on the right side. Roentgenograms of the lungs showed infiltration at the bases, as on the previous examinations.

One month after the patient's admission to the hospital ascites appeared for the first time. Paracentesis yielded 700 cc. of straw-colored fluid with a specific gravity of 1.008 and 300 cells per cubic millimeter, with 80 per cent lymphocytes and 20 per cent large mononuclear cells. Thereafter, fluid reaccumulated rapidly, and the abdomen was repeatedly tapped, several liters of fluid being removed on each occasion. Two weeks before the patient's death a diastolic murmur was noted in the third interspace on the left side. After four and one-half months of progressive emaciation and continued fever, the patient died, probably as a result of toxemia and cachexia.

Postmortem Examination.—The diagnosis was polyserositis (chronic adhesive pericarditis, bilateral adhesive pleuritis, perihepatitis, perisplenitis and peritonitis); anasarca; nonbacterial thrombotic endocarditis of the pulmonic and aortic valves; chronic interstitial pneumonitis; pulmonary emphysema and arterial sclerosis; degenerative encephalopathy; synovitis; osteoporosis of the fifth, sixth and seventh ribs of the right side and of the sixth rib on the left side; chronic passive congestion of the liver, kidneys, lungs and spleen; brown atrophy of the myocardium with focal fibrosis, and hemosiderosis of the pancreas.

There was marked emaciation. Scars of repeated paracentesis were present. The abdomen was protuberant, the umbilicus pouting. The third, fourth and fifth fingers of the left hand were in palmar and phalangeal flexion. There was slight edema of the lower extremities. Considerable ascites was noted. There were thickened adhesions binding the liver and spleen to the diaphragm, gallbladder and colon. The peritoneum was thickened. The liver was small and firm and was covered by numerous icy gray-white edematous adhesions over the diaphragmatic surface resembling the zuckergussleber. The liver had a nutmeg appearance, owing to passive congestion. The spleen had a thickened, edematous capsule and was purplish red on section. The gastro-intestinal tract showed passive congestion. The pancreas showed hemosiderosis. The pleural cavities were sealed by adhesions, and there were similar adhesions between the pleura, the pericardium and the mediastinum. The fifth, sixth and seventh ribs were adherent to the scapula. The lungs were atelectatic and showed markedly thickened septums, which appeared as an irregular network of grayish white streaks.

The pericardium was completely adherent. The heart was of normal size. On the closure line of the posterior cusp of the mitral valve was superimposed a pyramidal ridge, on which was a row of slightly raised yellowish verrucae the size of a pinhead. A similar row of verrucae was present on the aortic cusp of the same valve. At the commissure between the right and the left cusp of the aortic valve there was an unusual tawny gray, friable, rather massive conglomerate verrucous deposit, somewhat larger than a pea. A similar massive vegetation was present between the right and the posterior cusp of the pulmonary valve. The

myocardium showed some tigering and fibrosis. Examination of the right knee joint revealed edema of the capsular tissue. Synovia was removed for microscopic study.

Microscopically there was organizing pericarditis. Corresponding to the gross vegetations were some large blood platelet thrombi (fig. 2) which were undergoing early organization at the bases and which were slightly endothelialized at the edges. There was no valvular reaction to the verrucae. The cusps and rings were apparently normal. No auricular lesion or Aschoff bodies were present. The smallest blood vessels in the myocardium showed thickening, intimal proliferation (fig. 3), hyaline and granular plugs and recanalization. There was marked replacement fibrosis, probably secondary to vascular changes. There were many foci of lymphocytic infiltration.

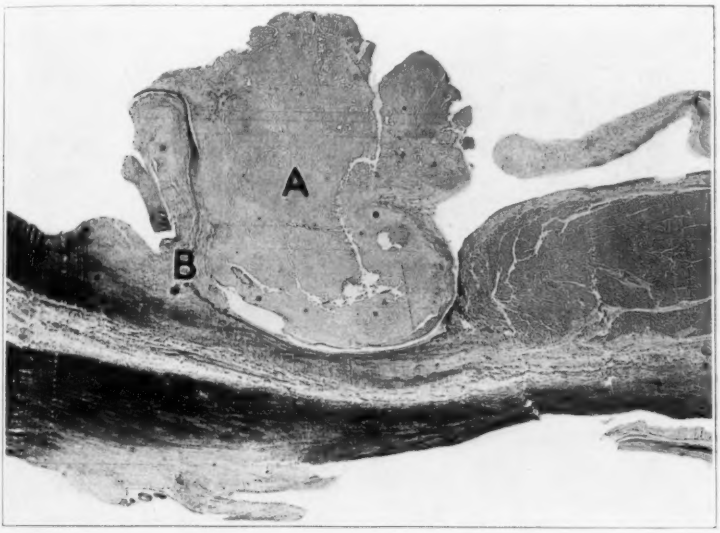

Fig. 2.—Nonbacterial thrombotic endocarditis of the aortic cusps. Weigert's elastic tissue stain and Van Gieson's connective tissue stain; low power. Section of the commissure of the aortic valve showing (*A*) a massive thrombus and (*B*) organization at the base of the thrombus. There is practically no inflammatory reaction in the cusp.

The kidney was cyanotic, and the glomeruli showed swelling and proliferation of endothelial and epithelial cells. Albumin could be seen in many of the capsular spaces. The blood vessels of the kidney showed only slight alteration. Sections of the synovial membrane showed loose and dense edematous connective tissue and fat. A large vein showed medial and adventitial infiltration with round cells and polymorphonuclear leukocytes and in one area degeneration of the media. There were other cellular infiltrations about smaller vessels.

Comment.—The outstanding clinical features in this case were the prolonged febrile course (three years) with persistently sterile blood cultures, the onset with acute polyarthritis, the development of deformities of the joints, particularly those of the fingers, and the presence of pleural and pericardial rubs, persistent physical signs and roentgen evidence of chronic pneumonitis, pleural effusion and possible pericardial effusion, recurrent ascites with little or no edema, questionable endocardial involvement, clinical symptoms of nephritis without elevation of the blood pressure and without impairment of the renal function, progressive emaciation and anemia.

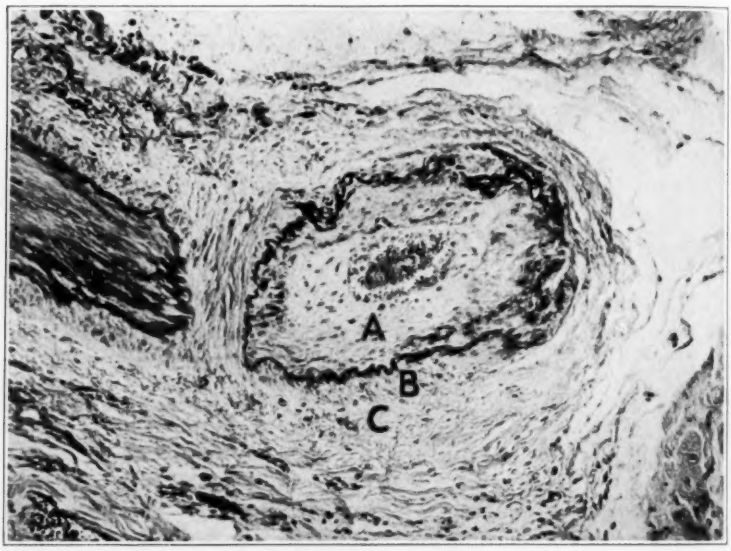

Fig. 3.—A vascular lesion in the posterior papillary muscle of the left ventricle of a patient 24 years old. Weigert's elastic tissue stain and Van Gieson's connective tissue stain; medium power. Section showing (*A*) marked intimal proliferation, (*B*) the media and (*C*) the adventitia.

Early in the course of the disease the striking migrating polyarthritis and high temperature were suggestive of acute rheumatic fever, especially when associated with pericarditis and signs of pulmonary involvement. On two occasions small nodules were noted on the dorsum of the wrist and on the elbow, but biopsy of one of these nodules gave no confirmation of rheumatic infection, and no other nodules were seen at the sites commonly involved in rheumatic fever. Furthermore, the prolonged atypical course, the failure to respond to salicylates, the uncer-

tainty of endocardial involvement despite recurrent arthritis, the unusual pulmonary signs, the symptoms of nephritis and the development of spindle-shaped deformities of the joints of the fingers cast considerable doubt on the diagnosis of rheumatic fever.

Another consideration was some form of tuberculosis, in support of which were the long-standing pulmonary involvement with fever, symptoms of pleuritis and pericarditis, the adenopathy, the spindle-shaped joints, the positive reaction to tuberculin and the absence of leukocytosis during the major part of the febrile course. The articular involvement was interpreted as a form of arthritis in the course of tuberculosis (Poncet). Against the diagnosis of tuberculosis, however, was the basal location of the pulmonary signs, the absence of cough or sputum, the absence of bacilli in the sputum and the negative results of inoculations of guinea-pigs. Finally, because of the prolonged septic course, the absence of positive results of blood cultures, the involvement of numerous organs, the renal phenomena, the appearance of two subcutaneous nodules and the generally atypical course, some unusual condition like periarteritis nodosa was considered. The positive Wassermann reaction was believed to be a coincidental finding.

Postmortem examination revealed no evidence of tuberculosis or rheumatic fever. The outstanding change was widespread inflammation and adhesions of the various serous cavities and obliteration of the pleural and pericardial cavities. The adhesions over the liver gave it the characteristic *Zuckerguss* appearance. The heart revealed peculiar thrombotic verrucae of nonspecific character at the commissures of the aortic and pulmonary valves. The smaller arteries and veins of the myocardium likewise showed nonspecific alterations. Despite the renal symptoms, renal disease was slight.

Case 2.—E. E., a 48 year old woman, was admitted to the Mount Sinai Hospital, service of Dr. B. S. Oppenheimer, on Sept. 16, 1928, and died on November 16.

History.—Three years before her admission to the hospital, this patient began to suffer from rheumatic symptoms, consisting of pain and swelling of the joints (fingers, wrists, knees, ankles) which persisted irregularly. Three months before her admission to the hospital a physician attended her for arthritis associated with fever, and at that time he heard a definite pericardial rub. Shortly afterward she seemed to suffer some cerebral episode with syncope and transient palsies of the cerebral nerves. She was taken to the Fordham Hospital, where she remained for four weeks with a temperature between 101 and 103 F., marked arthritis and progressive anemia. Since then she had suffered from frequent sore throats, weakness, shortness of breath, palpitation and occasional presternal pain. Her appetite had been poor, and she had lost weight.

Examination.—The patient was a pale woman, somewhat orthopneic, who complained of weakness. There was slight exophthalmos, and the scleras were blue. At the bases of both lungs there were dulness on percussion, absent tactile

fremitus and diminished breath and voice sounds. The area of cardiac dulness was considerably increased, the apex being situated 10 cm. to the left of the midline in the fifth interspace. The cardiac rate was 120 per minute. The first sound at the apex was snapping and was followed by a short systolic murmur. There was a rough systolic murmur over the pulmonic area, and the second sound here was accentuated and louder than the second aortic sound. The abdomen appeared tense, and the liver was palpable and somewhat enlarged. The abdominal reflexes were absent. There was incomplete extension of both elbow joints due to partial anklyosis. Tenderness and pain were noted on motion of both elbow joints. The right elbow was hot, red and swollen. The left wrist joint was painful. There was a Babinski reflex on the right. The temperature on admission was 104 F. The blood pressure was 106 systolic and 58 diastolic. The blood count showed 23 per cent hemoglobin, 1,530,000 erythrocytes, 11,900 leukocytes, 83.5 per cent polymorphonuclears, 14.5 per cent lymphocytes and 2 per cent monocytes. The Wassermann reaction of the blood was negative. The urine showed a trace of albumin, leukocytes and occasional granular casts. The urea nitrogen content of the blood was 17 mg. per hundred cubic centimeters. The phenolsulfonphthalein test showed 20 per cent excretion in two hours.

The tentative diagnosis was chronic rheumatic cardiovalvular disease, subacute bacterial endocarditis, chronic infectious arthritis and severe secondary anemia, with intra-abdominal neoplasm to be ruled out.

Course.—Despite the suggested diagnosis, the nature of the condition was still considered obscure after two weeks of observation. The course continued to be febrile, the temperature oscillating between 99 and 103 F. Repeated blood cultures remained sterile. On three different occasions white-centered petechiae were observed in the palpebral conjunctivae. Roentgen examinations made on several occasions showed small pleural effusion of the right side of the chest and of the left pleural cavity and once bilateral thickening of the pleura, without any other abnormality. The physical signs in the chest remained practically the same. Aspiration of the pleural cavities was nonproductive. Roentgen examination of the elbows, wrists, knees and ankles showed a moderate degree of hypertrophic arthritis. Electrocardiographic examination showed simple tachycardia and inversion of the T wave in the third lead. The patient finally died of anemia and cachexia. Despite the negative results of blood cultures and because of the febrile, "septic" course, the severity of the anemia and the white-centered petechiae, which were considered to be embolic, a diagnosis of subacute bacterial endocarditis was considered most likely, although the exact nature of the disorder remained obscure up to its termination.

Postmortem Examination.—The diagnosis was subacute polyserositis, nonbacterial thrombotic endocarditis of the mitral and tricuspid valves, acute bronchitis, disseminated sclerosing encephalomalacia, acute splenic tumor, infarcts of the spleen, parenchymatous degeneration of the kidney and liver, diffuse endarteritis with thrombosis and recanalization and arthritis with deformity.

Pallor and emaciation were marked. The periarticular regions of the joints as well as the joints themselves were markedly swollen. The swelling was especially marked in the right knee, both elbows and both ankles. The cavity of the right knee joint had a markedly thickened, whitish, glossy capsule and contained 25 cc. of dirty yellow fluid. Microscopically, the inner surface of the joint cavity showed proliferation of the endothelium. It was covered in several places by fibrinoid material. Beneath this layer was cellular infiltration consisting of polymorphonuclear leukocytes, lymphocytes, mononuclear cells and occasional giant cells. The stroma was edematous and contained a few gram-positive cocci.

Both pleural cavities were practically obliterated by adhesions involving the visceral and parietal layers on all the surfaces of the lungs. The lungs themselves were practically normal. The bronchi were congested with a red frothy fluid and mucus. The heart and pericardium weighed 510 Gm. The pericardium presented a glossy whitish icing of adhesions. The parietal pericardium was intensely edematous and thickened about ½ inch (1.3 cm.). It was extremely adherent throughout and was separated with difficulty from the thickened, edematous white visceral layer. The heart did not appear enlarged. On the mitral valve was an irregular, confluent row of yellow, friable granular vegetations the size of a pinhead, situated along the closure line but overhanging so as to reach to the free edge of the valve. Similar rows of vegetations were present on the tricuspid and aortic valves. There was no evidence of valvular deformity. Microscopic examination revealed blood platelet thrombi on the auricular surface of the mitral and tricuspid valves and on the ventricular surface of the aortic valves. The thrombi were partially vascularized and were undergoing organization. In the case of the aortic and tricuspid valves there was little or no reaction within the valve. In the mitral valve there was considerable cellular infiltration, including polymorphonuclear leukocytes, plasma cells and fibroblasts. There was slight evidence of necrosis. The appearance of the mitral valve bore some resemblance to that seen in atypical verrucous endocarditis. The ring of the mitral valve showed an inflammatory lesion suggestive of rheumatic fever. The lesion was rather more severe than that seen in atypical verrucous endocarditis. The rings of the aortic and tricuspid valves showed infiltration with mononuclear cells. There were no acute auricular lesions, Aschoff bodies or Bracht-Wächter lesions in the myocardium.

The peritoneal cavity contained about 300 cc. of clear yellowish fluid. There was widespread involvement of all the intestinal loops by extensive thin dull white irregular adhesions. The liver was adherent throughout its entire peritoneal surface to the adjacent peritoneum. The spleen showed similar adhesions. The liver was congested and showed granular areas of degeneration. On microscopic examination there was an exudate of fibrin and leukocytes on Glisson's capsule with partial organization of the exudate. The spleen weighed 420 Gm. and showed dull white patches resembling infarcts. Microscopically, there were wide areas of necrobiosis. The kidneys showed punctuate hemorrhages. The capsule stripped with difficulty. Microscopic examination showed marked perivascular infiltration with glia cells and pigment-laden gitter cells and gliosis in the region of blood vessels. The small arteries of the heart, lungs, pancreas, thyroid gland and spleen showed endothelial proliferation and hyaline and granular plugs (fig. 4) with organization and recanalization.

Comment.—The main features of this case were the prolonged febrile course (at least six months and probably longer) with sterile blood cultures, the long period of recurrent acute polyarthritis (three years) with deformities, the pericardial rub, the evidence of pleural effusions, the marked secondary anemia (23 per cent hemoglobin), the cerebral attack and the occasional white-centered petechiae in the conjunctivae. Because of the predominant arthritic symptoms at the onset, rheumatic fever was considered the likely diagnosis. However, the unusual course of the arthritis together with the development of deformities as well as the indefiniteness if not absence of valvular disease,

and the occurrence of white-centered petechiae made this diagnosis unlikely. With the appearance of petechiae and the continued septic course a diagnosis of subacute bacterial endocarditis was entertained, although the persistence of sterile blood cultures was disconcerting. Definite embolic phenomena other than the petechiae did not appear.

At postmortem examination there were subacute polyserositis with obliteration of the pleural and pericardial cavities and fluid and adhesions throughout the peritoneum. There was a slightly reactive nonrheumatic thrombotic endocarditis of the aortic and tricuspid valves. There were rather extensive vascular lesions consisting of endothelial proliferation

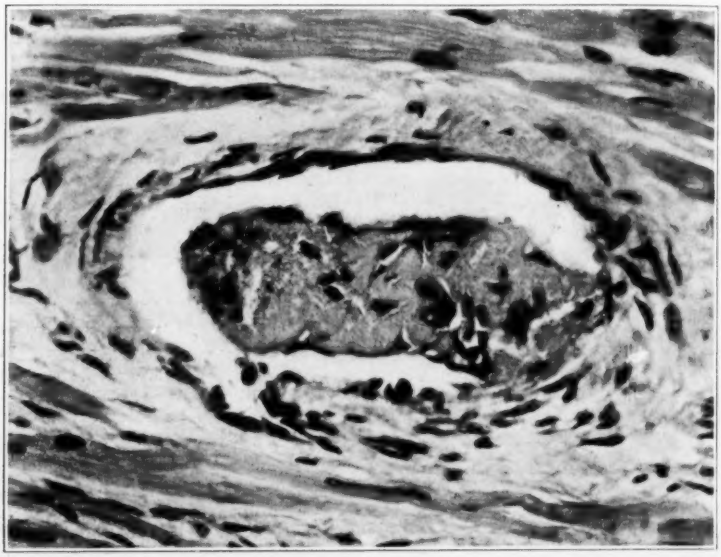

Fig. 4.—A vascular lesion in the posterior papillary muscle of the left ventricle. Hematoxylin and eosin stain; high power. The small artery has a large granular plug projecting into its lumen. Note the attachment to the vessel wall at one end and the endothelialization of the free margins.

of the smallest arteries with hyaline and granular plugs and recanalization of the lumens. As in the first case, there was no definite evidence of either tuberculosis or a recent rheumatic infection. The ring lesion in the mitral valve was suggestive of rheumatic infection, but the absence of auricular lesions or of Aschoff bodies, the slightly reactive nonbacterial thrombotic endocarditis of the tricuspid and aortic valves and the atypical valvulitis of the mitral valve were opposed to a rheumatic etiology.

The possibility of an atypical verrucous endocarditis was not considered clinically in this case. Nevertheless, certain features were highly suggestive: the arthritis, the febrile course, the histology of a pericardial rub and the white-centered petechiae. Pathologically, the valvulitis in the mitral valve also suggested this diagnosis. There were, nevertheless, adequate reasons for not including the condition under that category. The history of arthritis (three years) was of much longer duration than is customary, and the development of ankylosis and deformities has not thus far been encountered in that disease. Other than isolated petechiae, there were none of the cutaneous lesions usually observed. Certain gross and microscopic features of atypical verrucous endocarditis were absent. Thus, there were no flat, spreading lesions and no tendency to involve the valvular pockets or the mural endocardium. Furthermore, there was little reaction in the valves which were the seat of vegetations. Renal lesions were absent. Finally, the involvement of serous membranes appeared to be more conspicuous and widespread than that reported in atypical verrucous endocarditis.

Case 3.—M. K., a 19 year old Irish waitress, was admitted to the Mount Sinai Hospital, in the service of Dr. G. Baehr, on June 4, 1928, and died on October 8.

History.—Pain, redness and swelling of the ankles developed six months before the patient's admission to the hospital. The pain was severe enough to prevent her from walking and to require rest in bed for five weeks. During that time she suffered an attack of appendicitis and intestinal obstruction. The appendix was removed at another hospital. She felt well until two months before her admission to the Mount Sinai Hospital, when she began to suffer from breathlessness and palpitation. In the last three weeks fever, weakness and marked pallor had developed. She was treated by one physician for renal disorder, and by another for pleurisy with effusion. There was considerable loss of weight.

Examination.—The patient was pale, poorly nourished, poorly developed and acutely ill. Dyspnea and orthopnea were moderate. The face was puffy, but there was no actual edema. The breath was urinous. The area of cardiac dulness was considerably enlarged to both the right and the left. The apical impulse could not be felt. The cardiac rate was rapid. There was a short systolic murmur over the precordium. There was dulness to percussion at the base of each lung below the angle of the scapula. At the base of the right lung there was absence or diminution of tactile fremitus, with egophony and absence of breath sounds. At the base of the left lung there was diminished tactile fremitus with egophony and diminished breath sounds. Over the upper portion of the right lung posteriorly there was bronchovesicular breathing with a few moist and crepitant râles and increased tactile fremitus. Over the upper portion of the left lung posteriorly there was bronchovesicular breathing but no râles. In the left axillary region there were bronchovesicular breathing and many moist râles. The abdomen was essentially normal. The blood pressure was 106 systolic and 60 diastolic. The urine had a low specific gravity and contained considerable albumin, hyaline and granular casts, leukocytes and occasional erythrocytes. The urea nitrogen content was 41 mg. per hundred cubic centimeters of blood.

The tentative diagnosis was subacute glomerular nephritis with azotemia, bronchopneumonia, bilateral pleural effusion and pericardial effusion (?).

Course.—There was persistent fever during the four months of the patient's stay in the hospital, with only brief remissions. The temperature ranged between 99 and 103 F., occasionally reaching 104 or 105 F. Two days after the patient's admission to the hospital a pericardial rub was heard, which persisted on and off for two weeks. The patient was then considered to have severe rheumatic disease affecting both the cardiac and the pulmonary structures. Roentgenograms confirmed the presence of pleural effusion and revealed some general enlargement of the cardiac outline. A definite pleural rub was heard on the left side two months after the patient's admission and at the base of both lungs shortly before her death. On one occasion seven weeks after her admission to the hospital there was a recurrent attack of arthritis with marked pain in both knees and ankles, accompanied with high fever and sore throat. A week later the right knee became swollen, red and tender, and shortly afterward there was similar involvement of the elbows and wrists. Electrocardiograms showed left axis deviation with an inverted T wave in the third lead and tachycardia (pulse rate of 116). Six blood cultures were made for aerobic and anaerobic organisms during the course of the illness, but they were all sterile. A systolic murmur was heard at various times during the course of the disease, but at no time was there any certainty as to the presence of valvular disease. There was considerable evidence of renal involvement. There was persistent albuminuria associated with hyaline and granular casts, leukocytes and red blood cells in the urine. The urea nitrogen content rose to 71 mg. per hundred cubic centimeters of blood. The specific gravity of the urine was 1.016. A phenolsulfonphthalein test showed 20 per cent excretion in two hours. The albumin content of the blood was diminished to 2.5 per cent, with inversion of the albumin-globulin ration. In spite of transfusions there was progressive anemia, the hemoglobin content dropping to 34 per cent with 2,080,000 red blood cells per cubic millimeter of blood. There was never any leukocytosis, the leukocyte count at no time rising above 10,400 and generally remaining around 7,000 per cubic millimeter of blood. The sedimentation rate was rapid (eighteen minutes). The Wassermann test of the blood was negative. During the last month there was persistent abdominal pain which was difficult to control. Toward the end bilateral ulnar neuritis developed. Death occurred with pulmonary infarction and edema.

Postmortem Examination.—The diagnosis was nonbacterial thrombotic endocarditis (mitral and aortic valves), necrotizing arteritis, chronic fibrous pericarditis and pleuritis, anasarca, subacute encephalopathy, pulmonary edema and bronchopneumonia, multiple anemic infarcts of the spleen, necrosis of the kidney and pancreas and fatty degeneration of the liver.

The body was that of a pale, poorly nourished young woman. Both pleural cavities contained several hundred cubic centimeters of straw-colored fluid. There were universal edematous adhesions between the parietal and visceral pleurae which were easily separated. There were large areas of bullous edema on the visceral pleura, especially on the diaphragmatic surface, where fibrous adhesions almost completely obliterated the pleural space. The diaphragm was edematous and thickened on its pleural aspect. On cut section the lung presented an edematous surface with deep red wedge-shaped areas of hemorrhage. Microscopic examination showed pulmonary edema and areas of bronchopneumonia.

The heart weighed 425 Gm. The parietal pericardium was adherent to the heart. It was markedly thickened and was stripped from the epicardium with

difficulty, revealing edematous pale fibrous strands between the surfaces. The pericardial space was represented by flat sacculated cavities. At the middle of the posterior cusp of the mitral valve, extending from the closure line to the free border, was a firm mushroom-shaped vegetation, about 1 cm. at its widest extent, with a yellow, granular appearance. It was attached to the cusp by a narrow stalk. At the closure line of the anterior cusp there was a similar yellowish granular vegetation about 3 mm. in width. The aortic valve presented two unusual vegetations situated at the commissures between the left and right and the left and posterior cusps, respectively (fig. 5). They appeared like grayish yellow mounds of confluent smaller verrucae, with a rather friable surface and firm base. They were much larger than the vegetations in rheumatic disease, being about 8 mm. in diameter. On the posterior mitral valve was a soft adherent vegetation about the size of a cherry pit, and along the closure line was a small row of pinpoint-sized translucent pinkish vegetations.

Fig. 5.—Nonbacterial thrombotic endocarditis of the aortic cusps. The arrow points to a large friable vegetation on the right-posterior commissure.

Microscopically there was organizing pericarditis. The verrucae consisted of blood platelet thrombi undergoing organization. In the mitral valve the thrombotic material was fused with superficial valvular substance which was undergoing eosinophilic change. There was evidence of only a slight reaction in the valve substance. The ring of the tricuspid valve showed a few polymorphonuclear leukocytes and lymphocytes; otherwise it was normal. There was no evidence of rheumatic disease noted in the auricular endocardium, in the valves or in the myocardium. There was a moderate amount of replacement fibrosis in the myocardium, probably secondary to widespread necrotizing arteritis (fig. 6).

The peritoneal cavity contained 1 liter of clear straw-colored fluid. The kidneys showed marked congestion, yellow areas of infarction and flame-shaped hemorrhages throughout the cortex and medulla. Microscopic examination showed areas of hemorrhages and necrosis but only slight glomerular alterations. The liver showed an opaque, thickened, grayish capsule, passive congestion and fatty degeneration. The smaller arteries in the myocardium, kidneys, stomach and mes-

entery showed focal necroses with widespread inflammatory alterations. All the coats of the vessels were involved in the destructive lesion (necrotizing panarteritis).

Comment.—The onset of the disease in this case was accompanied with fever and polyarthritis six months before the patient's admission to the hospital. As in the preceding cases there was a persistent febrile course with sterile blood cultures. Pleural and pericardial rubs were heard during her stay in the hospital. There were clinical and roentgen evidences of pleural effusions and considerable evidence of subacute

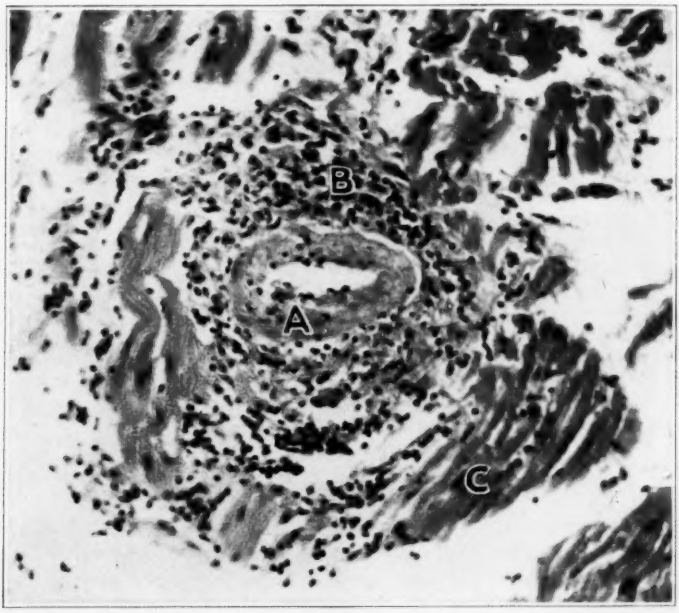

Fig. 6.—A vascular lesion in the left auricular myocardium. Hematoxylin and eosin stain; medium power. This section shows (*A*) necrosis, hyalinization and fusion of the intima and media, (*B*) perivascular leukocytic infiltration and (*C*) the myocardium.

nephritis with azotemia. Except for an inconstant systolic murmur, there was no reason to suspect valvular disease. Severe secondary anemia was present. Rheumatic fever was considered the most likely diagnosis, but the absence of valvular disease and the concomitant symptoms of nephritis confused the clinical picture. Postmortem examination revealed an organizing inflammatory lesion of the pericardium and pleura with fluid in the pleura, pericardium and peritoneum, nonbacterial thrombotic endocarditis, subacute encephalopathy and

diffuse vascular disease. The vascular disease in this case was more severe than in the preceding cases, showing necrosis and inflammation of all coats of the smaller arteries. The symptoms of nephritis were explained on the basis of vascular lesions in the kidneys.

CASE 4.—B. S., a 21 year old Puerto Rican woman, was admitted to the Mount Sinai Hospital on Feb. 23, 1930, and discharged on May 19. On October 24 she was readmitted, in the service of Dr. Baehr, and died on November 1.

History.—Pain had developed in the right lower quadrant of the abdomen one day before the patient's first admission to the hospital. There had been exposure to venereal disease a month before, followed by an increased vaginal discharge. On examination there was a roughened first cardiac sound with a blowing systolic murmur over the precordium. The blood pressure was 145 systolic and 100 diastolic. Marked tenderness was noted in the right loin, and fulness and tenderness were noted in the right vaginal fornix. There was a leukocytosis of 17,000, with 70 per cent polymorphonuclear leukocytes. Although the possibility of acute salpingitis or of visceral manifestation in Osler's disease was considered, a diagnosis of acute appendicitis appeared most likely. Operation was performed, and a normal appendix was removed. The fallopian tubes likewise were normal.

A review of the patient's history revealed that she had been suffering from polyarthritis for the past few months. The temperature was 101.6 F. on her admission to the hospital. The cardiac findings, the history of rheumatic pains and the fever combined to indicate a diagnosis of acute rheumatic fever. The temperature soon rose to 103.4 F. There were signs of pneumonia at the base of the right lung. The urine was of low specific gravity and contained albumin and casts. On the palmar and plantar aspects of the tips of the fingers and toes, respectively, there appeared diffuse erythema, telangiectasia and petechiae. The temperature remained between 103 and 104 F. for four and a half weeks and then gradually subsided. Blood cultures were sterile. One week after the patient's admission to the hospital there was a definite pericardial rub which persisted for four days. Then a pleural rub developed at the base of the right lung. At various times there were signs of fluid in both pleural cavities, especially on the right, but aspiration yielded none. There were physical signs of widespread infiltration of the entire right lung and of the lower lobe of the left lung. The specific gravity of the urine was 1.018. There was moderate secondary anemia (hemoglobin, 58 per cent; erythrocytes, 4,000,000 per cubic millimeter). There was recurrent arthritis of both knees and of the left elbow one week after the patient's admission to the hospital. The Pirquet test showed a negative result. The Wassermann test of the blood was negative. An electrocardiogram revealed inversion of the T wave in the third lead and a low T wave in the first and second leads. The record was interpreted as indicating poor myocardial function. Certain observers heard a diastolic murmur at the apex of the heart. With subsidence of the fever and the regression of the pulmonary signs, the patient was considered well enough to be sent to the country for convalescent care.

After discharge from the hospital the patient occasionally felt feverish and suffered from night sweats. Her strength did not increase. Pain developed in the left side of the chest and was aggravated by respiration. She had a severe chill on the day before her readmission to the hospital. She appeared chronically ill, the eyelids were puffy and there was pallor of the mucous membranes. There was a small exudate in the right fundus of the eye. The heart rate was irregular and rapid. There was no apparent cardiac enlargement. There was a long sys-

tolic murmur over the pulmonic area. The blood pressure was 126 systolic and 92 diastolic. There was a thick purulent vaginal discharge. Smears of material from the cervix, vagina and urethra showed no gonococci. The temperature was 101.8 F. The hemoglobin value was 54 per cent. There was marked asthenia. The patient was considered to be suffering from subacute bacterial endocarditis in the bacteria-free stage or from generalized tuberculosis.

The patient's condition became progressively worse. Three days after her second admission to the hospital she appeared to be in a state of vasomotor shock, for which there was no obvious cause. The possibility of cerebral embolus or of long-standing toxemia was considered. Persistent vomiting with alkalosis and tetany due to the vomiting developed, and the patient died one day later.

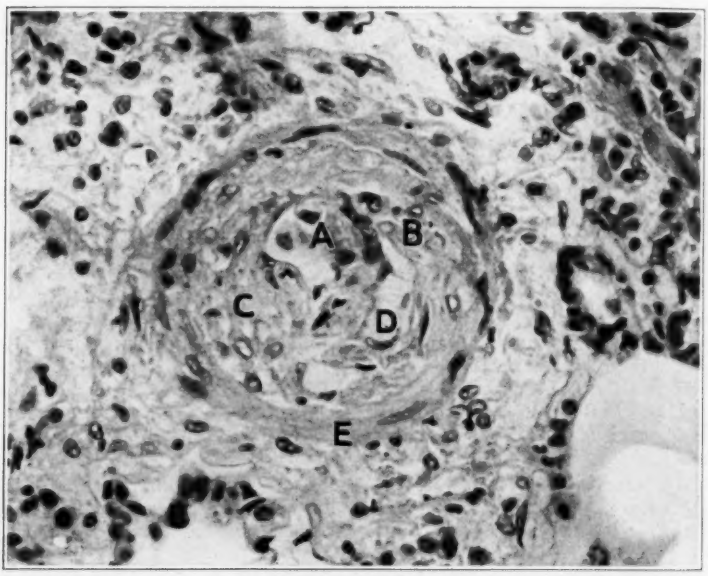

Fig. 7.—Vascular lesion of the lung (channeled vessel). Hematoxylin and eosin stain; high power. This section shows (*A*) proliferation of the endothelial cells with swelling and early granular degeneration, (*B*) intimal proliferation still showing swollen granular cells, (*C*) proliferated intima with replacement of the granular cells by scar tissue, (*D*) a canalized lumen and (*E*) the media.

Postmortem Examination.—The diagnosis was chronic valvular disease (slight mitral stenosis), chronic polyserositis, nonbacterial thrombotic endocarditis of the mitral valves, meningo-encephalitis (nonsuppurative), diffuse endarteritis, infarcts of the spleen and kidneys, fatty degeneration of the liver, petechiae of the mesentery and omentum and follicular hyperplasia of the gastro-intestinal tract.

The body was that of an emaciated, pale young woman. Both pleural cavities were filled with firm adhesions. The pleural surfaces were everywhere roughened by adhesions, which were separated with difficulty. Adherent pericarditis was universal. The pleuropericardial space was obliterated by adhesions. On the

anterior cusp of the mitral valve was a continuous narrow ridge of confluent friable vegetations; a similar but discontinuous yellow ridge was present on the posterior cusp. Microscopically there was organizing pericarditis. There was a blood platelet thrombus on the mitral valve superimposed and combined with a superficial valvular substance showing eosinophilic change. There was low grade lymphocytic valvulitis of the mitral valve, some thickening of the cusp and a mild inflammatory lesion of the ring. However, there were no rheumatic auricular lesions and no Aschoff bodies, and the valvulitis was not that of active rheumatic infection. The appearance of the mitral valve was interpreted as that of non-bacterial thrombotic endocarditis on a somewhat thickened cusp which had undergone some previous inflammatory, possibly rheumatic alteration.

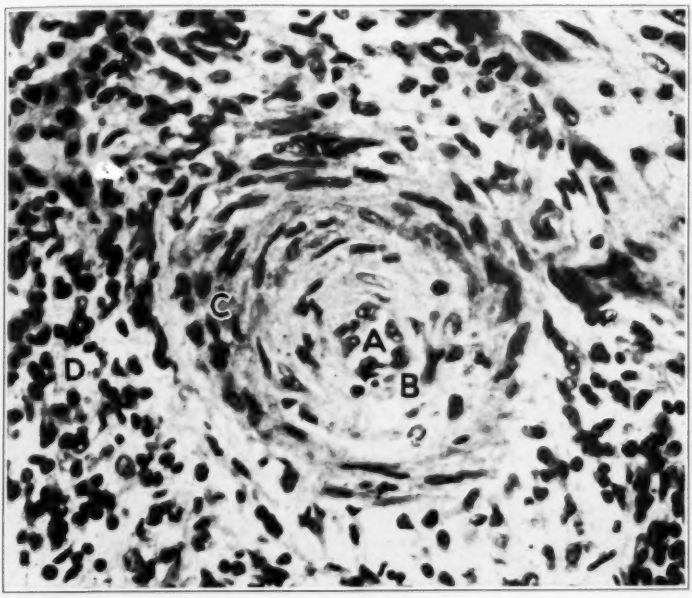

Fig. 8.—Vascular lesion of the lung. Hematoxylin and eosin stain; high power. This section shows (*A*) a markedly narrowed lumen lined by swollen endothelial cells, (*B*) a proliferated intima still showing swollen granular cells, (*C*) a hypertrophied and edematous media and (*D*) perivascular lymphocytic infiltration.

The pulmonary artery was considerably dilated. The peritoneal cavity contained a fairly large quantity of clear amber fluid. There were adhesions between the liver and the inferior surface of the diaphragm and between the spleen and the diaphragm. Loops of ileum and cecum were adherent to the uterus and the right ovary. The cecum and ascending colon were adherent to the lateral wall of the peritoneal cavity. The kidneys showed coarse granulation due to depressed scars of infarction. The glomerular epithelium showed enlargement and proliferation. Thickening and infiltration of the meninges were noted. There were con-

siderable vascular alterations throughout several organs. The capillaries and smaller arteries of the heart showed intimal thickening and in places partial or complete occlusion of the lumen. This appeared to be due to swelling and proliferation of endothelial cells with granular degeneration and fusion. In the process of organization these granular plugs formed marked intimal thickening or occlusion with canalization. Lymphocytic infiltration occurred around these vessels. Similar alterations were present in the vessels of the kidney, stomach, pancreas, brain and lung (figs. 7 and 8).

Comment.—The essential features in this case were the febrile illness lasting for almost a year with only a brief intermission, sterile blood cultures, polyarthritis, pleural and pericardial rubs with signs of pleural effusion, symptoms of nephritis, secondary anemia, abdominal symptoms resembling appendicitis and cerebral complications. With the discovery of symptoms of arthritis the patient was considered to be suffering from rheumatic fever. However, long-standing fever and evidences of nephritis suggested that this might be a case of subacute bacterial endocarditis with sterile blood cultures. Postmortem examination revealed, as in the previous cases, inflammation of the serous membranes lining the pleura, pericardium and peritoneum, a nonbacterial, nonrheumatic thrombotic endocarditis, diffuse endarteritis with plugging and canalization of vessels and subacute nonsuppurative encephalitis. The nonbacterial thrombotic endocarditis was superimposed on an old rheumatic valve, a relationship emphasized in our general description of this form of endocarditis.[1]

COMMENT

Clinical Features.—Certain manifestations were present in all these cases. The patients were women, three of them being about 20 years of age and one 48. For the most part, the clinical course was that of a general infection, but numerous aerobic and anaerobic blood cultures were persistently sterile. The course of the disease was prolonged and progressive, and except for brief remission there was persistent fever during the entire period of the illness (in one case for three years).

The onset was usually marked by acute polyarthritis involving both the large joints and the small joints of the fingers and hands. A striking feature was the development in two of the four cases of marked joint deformities with a spindle-shaped appearance of the fingers, as in chronic infectious arthritis, tuberculosis or syphilis.

Early in the course of the disease a pericardial rub was heard in all four cases and a pleural rub in three cases. There were physical and roentgen signs of pleural effusions in all instances. Although rather large quantities of ascitic fluid were found in every case at postmortem examination, this was verified by aspiration only once during life.

There was never striking evidence of endocardial involvement. A systolic murmur was generally present. The electrocardiographic

changes were compatible with adhesive pericarditis. Marked secondary anemia was a prominent feature. Despite persistent fever, leukocytosis was never marked. Urinary abnormalities were frequent. Albumin and casts were regularly present, and leukocytes and erythrocytes were generally noted. There was evidence of renal impairment only in the third case. Death resulted from increasing toxemia, anemia and cachexia.

Pathologic Condition.—Inflammatory changes were present not only in the pericardium, the pleurae and the peritoneum but also in the serous lining of the joint spaces in the two cases in which these were available for examination. There were marked pleural and pericardial adhesions, generally with obliteration of the respective cavities but occasionally with remnants of effusions. In the peritoneal cavity were noted a large amount of clear ascitic fluid, fine or firm adhesions binding the loops of intestine to each other or to the parietal peritoneum (without intestinal obstruction) and generally perihepatitis and perisplenitis with adhesions to neighboring structures. The synovial membranes of various joints, in the two cases in which these were available for examination, were thickened and edematous and showed marked endothelial hyperplasia and cellular inflammation, with occasional perivascular infiltrations.

In each case the heart showed nonbacterial thrombotic deposits on one or more of the valves of the type described in detail elsewhere.[1] These vegetations consisted of a conglomeration of blood platelet thrombi deposited on a valve which had undergone eosinophilic change, with little or no inflammatory reaction in the valve itself.

Vascular alterations were observed in every case. In the first case these were mild and consisted of occasional endarteritis and endophlebitis of the smallest vessels, particularly those of the myocardium. In the second case there was considerable thickening of the smallest arteries and arterioles of the lungs, myocardium, brain and thyroid gland, occasionally with marked narrowing of the lumens or complete obliteration by hyaline or granular plugs. Similar but more extensive changes were present in the fourth case, the vessels of the lung showing necrosis as well as inflammation. In case 3 there was marked necrotizing panarteritis involving the heart, kidneys, stomach and mesentery.

Diagnosis.—The onset with polyarthritis frequently led to a diagnosis of acute rheumatic fever. However, there was neither constant nor definite evidence of valvular disease despite the prolonged course. There were no electrocardiographic changes suggesting rheumatic fever. The early development of ankylosis and of articular deformity, with the production of spindle-shaped joints, is absent or rare in rheumatic fever. At postmortem examination there was no evidence of recent rheumatic infection.

The condition frequently simulated a general infection. Subacute bacterial endocarditis was a diagnosis frequently entertained. However, blood cultures were persistently sterile, and embolic phenomena were absent. Tuberculosis was sometimes considered because of the pleuropulmonary signs, the articular phenomena and the continued fever. These same symptoms resembled those of atypical verrucous endocarditis (Libman and Sacks). At postmortem examination the flat, spreading variety of vegetation, the involvement of mural endocardium and the severe inflammatory and necrotizing lesions in the valves described by Libman and Sacks [2] and by Gross [4] were absent in our cases.

Recently Baehr, Klamperer and Schifrin [5] described twenty-three cases of disseminated lupus erythematosus associated with extensive vascular lesions and frequently with endocarditis. Some of their patients showed features characteristic of the Libman-Sacks variety of endocarditis, while others revealed the nonbacterial thrombotic endocarditis noted in our cases. Baehr and his co-workers found that a high percentage of their patients had had arthritis and inflammation of the pleura and pericardium in addition to the vascular lesions and endocarditis. The absence of lupus erythematosus in our cases may not be an essential difference. It is conceivable that a condition belonging to the same general type as that described by Baehr and his co-workers might occur without the striking cutaneous lesions but with the other associated clinical and pathologic features of the disease. It should be added, however, that aside from the absence of lupus erythematosus in our cases, the articular manifestations were more marked and produced more conspicuous deformities than those that occurred only occasionally in the cases of Baehr and his co-workers, the involvement of the serous membranes was more extensive and dominated the clinical picture and the vascular lesions were not altogether identical. Two other cases similar to those here described and to those of Baehr, Klemperer and Schifrin were reported by Tremaine [6] and Christian.[7]

Etiology and Pathogenesis.—These cases appear to form a definite clinical syndrome of unknown etiology. The salient characteristic of the disease was its tendency to affect serous membranes (pleurae, pericardium, peritoneum and synovial membranes throughout the body) and the endothelial lining of the blood vessels and of the heart (endocardium). Certain clinical and pathologic features suggested an infec-

4. Gross, Louis, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, pp. 527-550.

5. Baehr, G.; Klemperer, P., and Schifrin, A.: Tr. A. Am. Physicians **50**: 139-155, 1935.

6. Tremaine, M. J.: New England J. Med. **211**:754-759, 1934.

7. Christian, H. A.: M. Clin. North America **18**:1023-1026, 1935.

tious process. The vascular lesions differed in many respects from those described by Wiesel,[8] Wiesner,[9] Siegmund[10] and others in a number of infectious diseases but resembled some of those observed in rheumatic fever (Gross[11]). In addition, extensive vascular lesions of the necrotizing variety, such as those present in one of our cases, have been described in association with rheumatic fever.[12]

The relationship of our cases to those of Libman and Sacks,[2] Baehr, Klemperer and Schifrin,[5] Tremaine[6] and Christian[7] must await the discovery of the specific etiology or the determination of definite rigid criteria for the clinicopathologic syndrome. Although the possibility that these are atypical cases of rheumatic fever cannot be entirely excluded, studies recently completed[13] indicate that they probably all comprise a definite clinical-pathologic syndrome. For the present it is important to draw attention to this group of cases so that the condition may be recognized clinically and may be studied for further elucidation.

SUMMARY

In a previous study on indeterminate forms of endocarditis cases of nonbacterial thrombotic endocarditis were described and classified. Certain groups appeared to possess clinical and pathologic features in common.

This report deals with one of these groups, comprising four cases, in which the disease was characterized by prolonged fever, polyarthritis, inflammation of serous membranes (pleura, pericardium, peritoneum, endocardium and synovial membrane) and a variety of vascular lesions.

The clinical course was that of a general infection, but cultures of the blood were sterile. The onset was marked by inflammatory polyarthritis involving the large and small joints. Ankylosis and deformities developed in two of the four cases. There were pleural and pericardial effusions. Symptoms of endocardial involvement were indefinite. Symptoms of renal and cerebral involvement were frequent. The differential diagnosis lay between a general infection, subacute bacterial endocarditis, rheumatic fever and tuberculosis.

8. Wiesel, J.: Wien. klin. Wchnschr. **19**:723-725, 1906.

9. Wiesner, R.: Wien. klin. Wchnschr. **19**:725-726, 1906.

10. Siegmund, H.: Zentralbl. f. allg. Path. **35**:276-277, 1924.

11. Gross, Louis; Kugel, M. A., and Epstein, E. Z.: Am. J. Path. **11**:253-279, 1935.

12. Friedberg, C. K., and Gross, Louis: Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, with a Note on Abdominal Rheumatism, Arch. Int. Med. **54**:170-198 (Aug.) 1934.

13. Friedberg, C. K., and Gross, Louis: The Cardiac Lesions in the Libman-Sacks Syndrome, with a Consideration of Its Relationship to Acute Diffuse Lupus Erythematosus, to be published.

At necropsy there were adhesive pleuropericarditis with obliteration of the pleural and pericardial cavities; an excessive quantity of fluid in the peritoneum; perihepatitis, and perisplenitis with adhesions between the liver and the diaphragm, between the spleen and the diaphragm, between the intestines and between the parietal and the visceral peritoneum. The synovial membranes, in the two cases in which these were available for examination, were thickened and edematous and showed marked endothelial hyperplasia and cellular inflammation with occasional perivascular infiltrations. The heart showed nonbacterial thrombotic deposits on one or more of the valves. There was no evidence that these were of rheumatic origin. There were a variety of vascular lesions in many organs, including endothelial proliferation, endothelial desquamation with granular degeneration and swelling, narrowing or obstruction of the lumen by plugs, intimal proliferation and actual necrosis of the vessel wall.

The clinical and pathologic features suggested that we were dealing with some infectious agent with a pronounced toxic effect on structures lined by endothelium.

PATHOLOGY AND PHARMACOLOGY OF CARDIAC SYNCOPE AND SUDDEN DEATH

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LOS ANGELES

Cardiac syncope is sudden loss of consciousness due to cerebral anemia of cardiac origin. Sudden "cardiac death" may be considered as fatal cardiac syncope.

PATHOLOGY OF CARDIAC SYNCOPE AND SUDDEN DEATH

Temporary loss of consciousness in cardiac disease is usually associated with complete heart block, i. e., the Adams-Stokes syndrome. Careful histologic examination of the myocardium is frequently required to discover the myocardial lesion, which consists in most instances of fibrosis affecting the junctional tissues. The remainder of the myocardium usually shows only minimal changes.

Sudden death is a prominent feature of disease of the coronary arteries. In a previous analysis [1] of 113 autopsies at which occlusive coronary disease was noted, the clinical picture was congestive heart failure in approximately 40 per cent and sudden death without congestive heart failure in 60 per cent. In most of the cases of the latter group the clinical syndrome of angina pectoris was presented. There are two essential features of angina pectoris: (1) attacks of pain, usually in the chest, and (2) a tendency to sudden, unexpected death. The literature contains considerable material on the nature, prevention and treatment of the attack but little on the mechanism and therapy of the other important feature, the sudden death.

An analysis was made of 142 autopsies showing occlusive coronary disease in which sudden death occurred. The purpose of this study was to determine the frequency of structural changes in the myocardium sufficient to explain the sudden death. Cases were excluded in which there was a history of congestive heart failure and in which there was evidence of passive congestion of the liver at autopsy. Cases were also excluded in which there was a history of acute dyspnea or pain, with death deferred for a variable period, and in which edema of the lungs was present at autopsy. This series consisted essentially of cases in

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1. Nathanson, M. H.: Disease of the Coronary Arteries, Am. J. M. Sc. **170**: 240, 1925.

which sudden death occurred at a time when the circulation was competent. The study is summarized in the tables 1 to 3.

Table 1 shows the age distribution by decades. The youngest patient was 26, and the oldest, 83, the average age at the time of death being 58.1 years.

Table 2 shows the weights of the hearts as recorded in 139 autopsies. Marked cardiac hypertrophy (600 Gm. or more) was exceptional, occur-

TABLE 1.—*Age Distribution of One Hundred and Forty-One Patients with Coronary Disease Terminated by Sudden Death*

Age, Years	Number of Cases	Percentage
20 to 30	1	0.7
30 to 40	5	3.6
40 to 50	24	17.0
50 to 60	40	28.3
60 to 70	53	37.5
70 to 80	16	11.3
80 to 90	2	1.4

TABLE 2.—*Weights of Hearts of One Hundred and Thirty-Nine Patients with Coronary Disease Terminated by Sudden Death*

Weight of Heart, Gm.	Number of Cases
200 to 299	2
300 to 399	55
400 to 499	47
500 to 599	31
600 to 699	4

The heart weighed less than 450 Gm. in 93 cases and more than 450 Gm. in 40 cases.

TABLE 3.—*Gross Structure of the Myocardium in Patients with Coronary Disease Terminated by Sudden Death*

	Number of Cases	Percentage
Normal	70	50
Fibrosis	31	22
Myomalacia cordis	30	21
Rupture of heart	11	7
Total	142	

ring in only 4 instances. In approximately two thirds of the cases the cardiac weight was less than 450 Gm. This analysis indicates that sudden death in cases of coronary disease is usually associated with a heart either normal in size or only moderately hypertrophied.

Table 3 gives an analysis of the gross structure of the myocardium in 142 cases. According to the gross appearance of the myocardium the cases were arbitrarily divided into four groups. In the group in which the myocardium is recorded as normal it was practically normal on section or showed only streaks of fibrosis. In the group in which

fibrosis was present, there was either extensive diffuse fibrosis or large localized patches of scarring. The remaining two groups consisted of cases in which the heart showed one or more recent infarcts or areas of softening and in which rupture of the heart had occurred.

It is apparent that only acute and extensive myocardial damage can account for the sudden change from a competent circulation to complete cessation of the circulation and death. Fibrosis of the myocardium may affect the efficiency of the heart to only a slight degree. It is well known that a large infarction frequently heals, permitting normal cardiac activity for a period of years, a large scar of the healed infarct being present at autopsy. Rupture of the heart, the only myocardial change which can definitely account for sudden death, was present in only 7 per cent of the cases at autopsy, indicating that a structural basis for sudden death is infrequent.

Table 4 shows the incidence of coronary thrombosis in 142 autopsies and its frequency in the four subgroups. Thrombosis of the large

TABLE 4.—*Incidence of Coronary Thrombosis in Patients with Coronary Disease Terminated by Sudden Death*

Gross Structure of Myocardium	Number of Cases	Cases of Coronary Thrombosis	Percentage
Normal	70	12	17.0
Fibrosis	31	6	20.0
Myomalacia cordis	30	15	50.0
Rupture of heart	11	6	54.0
Total	142	39	27.5

coronary branch occurred in 39 cases, or 27.5 per cent. As might be expected, the incidence was higher in the groups in which there was a more acute and severe degree of myocardial damage.

Comment.—Necropsy observations in cases of coronary disease failed to explain the sudden death in most instances. The heart was usually of normal size or only moderately enlarged. The structure of the myocardium in all cases, with the exception of a small group, was compatible with life and the continuance of a fairly efficient circulation. In most cases there was no evidence of acute obstruction of a large coronary branch. The necropsy evidence therefore indicates that the mechanism of sudden death in coronary disease is usually physiologic. It is to be emphasized that there are only two physiologic mechanisms within the heart which can account for a sudden cessation of the circulation leading either to temporary syncope or to death, namely, a cardiac or ventricular standstill and ventricular fibrillation.

PHARMACOLOGY OF CARDIAC SYNCOPE AND SUDDEN DEATH

The action of drugs on cardiac standstill and ventricular fibrillation was studied by pharmacologic methods which are applicable to man.

It is well known that ventricular standstill is the usual mechanism underlying the transient syncopal attacks of heart block. Although Allbutt [2] stated the belief that a vagus standstill of the entire heart is the cause of death in angina pectoris, the preponderance of evidence indicates that fatal cardiac syncope is usually due to ventricular fibrillation.

Cardiac Standstill.—In cases of complete heart block the ventricles, deprived of the influence of the sinus node, beat independently. The continuance of ventricular contraction is dependent on the rhythmic power of the ventricles. Being but poorly equipped with the property of rhythmicity, the ventricles at times fail to produce the necessary stimulus, and ventricular standstill and syncope follow. The therapeutic indication is the administration of drugs which will increase the rhythmic property of the ventricles. In previous reports [3] it was demonstrated

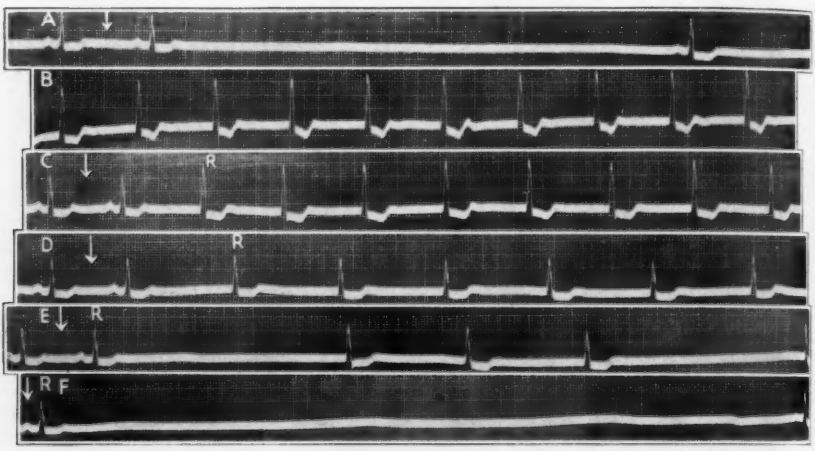

Fig. 1 (H. B.).—*A* shows a standstill of seven and six-tenths seconds induced by pressure on the right carotid sinus (arrow). *B* was taken one minute after the intravenous injection of 0.05 mg. of epinephrine and shows the standstill abolished by the development of ventricular rhythm. The lowest strip shows the disappearance of the effect after fifteen minutes.

that the cardiac standstill which can be induced in many human subjects by pressure on the right carotid sinus may be utilized for the study of the action of drugs on cardiac rhythmicity. The pressure on the carotid sinus in these cases eliminates the activity of the sinus node.

2. Allbutt, Clifford: Diseases of the Arteries Including Angina Pectoris, London, Macmillan & Company, 1915, vol. 2.

3. Nathanson, M. H.: Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch. Int. Med. **51**:387 (March) 1933; Further Observations on the Effect of Drugs on Induced Cardiac Standstill, ibid. **54**:111 (July) 1934.

Cardiac standstill follows, since no other portion of the heart possesses the rhythmic function to a sufficient degree for the development of a new pace-making center. It was demonstrated that after the administration of certain drugs cardiac standstill was not influenced, indicating that these substances were without effect on cardiac rhythmicity. Ineffective compounds were digitalis, caffeine, pyridine beta-carbonic acid di-ethylamine, metrazol, thyroxine and calcium gluconate. It was found, however, in 10 subjects that epinephrine (fig. 1), by initiating a new rhythmic center in the ventricles, exerts a powerful effect in the prevention of induced cardiac standstill. It was demonstrated that ephedrine (fig. 2) and other compounds related in structure to epinephrine also

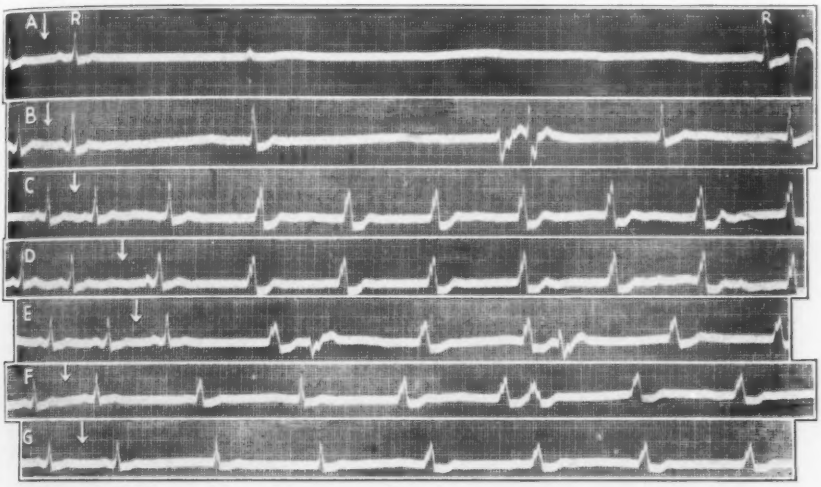

Fig. 2 (H. B.).—*A* shows an induced standstill of nine and six-tenths seconds. The lower strips were taken after 100 mg. of ephedrine sulfate had been injected intravenously. The standstill was abolished by the development of ventricular rhythm. The rate of the new pacemaker is similar to that following the administration of 0.05 mg. of epinephrine (fig. 1). This indicates that the ratio of the activity of ephedrine to that of epinephrine is 1 to 2,000.

had a definite action in increasing ventricular rhythmicity. It was possible to carry out a quantitative study of these compounds, and the intensity of the effect increased as these substances approached the composition of epinephrine itself. The effectiveness of the drugs of the epinephrine series indicates that the response of the heart is the result of a specific pharmacologic action, stimulation of the cardiac-accelerator mechanism, and only drugs possessing this action are likely to be effective in cardiac standstill.

Ventricular Fibrillation.—The preponderance of evidence indicates that while cardiac standstill is the basis for temporary cardiac syncope, ventricular fibrillation is the mechanism underlying the fatal syncope of coronary disease. The evidence may be summarized as follows:

1. Hering [4] has stated that in twenty years of experimental work on animals he has frequently observed standstill of the entire heart produced by stimulation of the vagus nerve. This is characterized by being of relatively short duration with a spontaneous return of activity. There is temporary circulatory insufficiency but not death. He said that he knew of no experiment in which the whole heart or the ventricles have been brought to a permanent standstill. Either the sinus node regains its activity or another focus acts.

2. In contrast to standstill, ventricular fibrillation in the experimental animal is usually a lethal arrhythmia, persisting until death. There is usually no return of a coordinated contraction. The collapse in cases of angina pectoris is just such an irreversible condition. In cases of heart block, on the other hand, the rule is repeated attacks with recovery.

3. Perhaps the most striking evidence correlating ventricular fibrillation and coronary disease is the high incidence of ventricular fibrillation following experimental ligation of the coronary arteries.

4. Extrasystoles and ventricular tachycardia, which may be considered as prefibrillation arrhythmias, are frequently observed associated with clinical evidence of acute coronary closure.

Although temporary cardiac standstill can be induced easily and with safety in human subjects, it is obvious that ventricular fibrillation may not be investigated in the same manner. The exact nature of ventricular fibrillation is not clear. There is considerable evidence, however, that cardio-accelerator nerve impulses and epinephrine play an important part in the genesis of this arrhythmia. Observations on experimentally induced ventricular fibrillation strongly indicate that epinephrine acts synergistically with some other factor to increase ventricular rhythmicity leading to ventricular fibrillation. Levy and Lewis [5] produced ventricular fibrillation in cats under light chloroform anesthesia by the injection of epinephrine.

Rothberger and Winterberg [6] found in dogs that stimulation of the accelerator nerves or the introduction of epinephrine induced ventricular

4. Hering, H. E.: Der Sekundenherztod mit bensonderer Berücksichtigung des Herzkammerflimmerns, Berlin, Julius Springer, 1917.

5. Levy, A. J., and Lewis, T.: Heart Irregularities Resulting from the Inhalation of Low Percentages of Chloroform Vapour, and Their Relationship to Ventricular Fibrillation, Heart **3**:99, 1912.

6. Rothberger, C. J., and Winterberg, H.: Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Acceleransreizung, Arch. f. d. ges. Physiol. **142**:461, 1911.

fibrillation in a heart partially poisoned with barium chloride. Otto [7] consistently produced ventricular fibrillation in dogs by ligation of branches of the coronary circulation. When the same procedure was carried out subsequent to section of the sympathetic fibers, ventricular fibrillation did not follow. Nahum and Hoff [8] found that inhalation of benzene regularly produced ventricular fibrillation and this did not occur in animals after adrenalectomy. More recently Hoff and Nahum [9] showed that removal of the stellate ganglions and adrenal glands enormously decreased the susceptibility of the ventricles to fibrillation following electric shock. These observations indicate that epinephrine is an important exciting agent in the development of fibrillation in a ventricular myocardium sensitized by various methods, such as poisoning with chloroform, barium chloride and benzene, reduction of the blood supply or application of electric stimuli. It appears, therefore, that the tendency to ventricular fibrillation should be lessened by the application of drugs which counteract the effect of epinephrine on the ventricles.

In the present clinical study epinephrine was introduced in doses sufficient to increase ventricular rhythmicity to the point of the development of an ectopic ventricular rhythm. The action of various drugs in the prevention of this rhythm was then observed. There is a relationship between these induced ventricular rhythms and ventricular fibrillation. Ventricular fibrillation in its fully developed form does not come on abruptly. First, the cardiac rhythm is disturbed by premature contractions of ventricular origin which increase in number until groups are formed. Other foci of activity are usually added. The heart then accelerates in response to these new impulses and is eventually controlled by them exclusively. A stage of rapid ventricular tachycardia originating from either a single focus or several ventricular foci frequently appears before the full development of the fibrillation. In the present study it was found that these types of ventricular rhythm could be induced in many human subjects by the intravenous injection of epinephrine. The induced ventricular rhythm represents a physiologic state in the ventricles similar to but of a lesser degree than that which exists in fibrillation. It is therefore evident that the action of drugs on the induced rhythm may be applicable to ventricular fibrillation.

7. Otto, H. L.: Untersuchungen über die Nn. accelerantes cordis, Arch. f. d. ges. Physiol. **217**:147, 1927.

8. Nahum, L. H., and Hoff, H. E.: The Experimental Production of Ventricular Fibrillation and Its Prevention by B-Methyl Acetylcholine Chloride, Am. J. Physiol. **109**:78, 1934.

9. Hoff, H. E., and Nahum, L. H.: The Nature of Ventricular Fibrillation Following Electric Shock and Its Prevention by Acetyl-B-Methylcholine Chloride, Am. J. Physiol. **110**:675, 1935.

EXPERIMENTS

The experiments were carried out in the following manner: Elderly persons were selected, and a control electrocardiogram was made in each case. Epinephrine hydrochloride, 0.1 mg., was then injected intravenously, and a continuous electrocardiogram was made for five minutes. In most cases frequent extrasystoles from multiple ventricular foci developed within one minute, with a return to the normal rhythm usually within four minutes following the injection. The drug to be studied was then administered; after a suitable period 0.1 mg. of epinephrine was again administered intravenously, and the reaction was observed in the electrocardiogram.

Quinidine.—This drug was used because of its well known action in the restoration of the normal rhythm in cases of auricular fibrillation and in the prevention of a return of the fibrillation. Quinidine acts also on ventricular muscle. Scott [10] and Levine and Fulton [11] found that quinidine was effective in the prevention and treatment of ventricular tachycardia. Dock [12] reported a case in which maintenance doses of quinidine prevented attacks of ventricular fibrillation. H. D. Levine [13] demonstrated that experimental ventricular fibrillation was inhibited by quinidine. Jackson, Friedlander and Lawrence [14] showed that quinidine tends to counteract the development of ventricular fibrillation after the administration of digitoxin and aconitine.

In 10 cases 0.1 mg. of epinephrine hydrochloride injected intravenously induced rapid extrasystolic arrhythmia from multiple ventricular foci. Quinidine sulfate was then administered orally in increasing doses for five or six days. On the last day of the experiment the amount usually administered was 2 or 2.2 Gm. in divided doses. In 2 cases the maximum amount administered was from 0.8 to 1 Gm. One hour after the last dose of quinidine was administered 0.1 mg. of epinephrine hydrochloride was injected intravenously. In 8 cases the ventricular extrasystoles were entirely eliminated, and the reaction was merely sinus tachycardia. In the 2 instances in which the smaller doses were administered an occasional extrasystole from a single ventricular focus developed (figs. 3 to 10). These observations indicate that quinidine

10. Scott, R. W.: Observations on a Case of Ventricular Tachycardia with Retrograde Conduction, Heart **9**:297, 1921.

11. Levine, S. A., and Fulton, M. N.: The Effect of Quinidine Sulphate on Ventricular Tachycardia, J. A. M. A. **92**:1163 (April 6) 1929.

12. Dock, W.: Transitory Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulphate, Am. Heart J. **4**:709, 1929.

13. Levine, H. D.: Effect of Quinidine Sulphate in Inhibiting Ventricular Fibrillation, Arch. Int. Med. **49**:808 (May) 1932.

14. Jackson, D. E.; Friedlander, A., and Lawrence, J. V.: Experimental Investigation of Pharmacological Action of Quinidine, J. Lab. & Clin. Med. **7**:311, 1922.

exerts a powerful action in the prevention of ventricular rhythm of a prefibrillation type.

Ergotamine.—It is well known that this drug paralyzes the ends of the sympathetic nerves and in the experimental animal counteracts and even reverses the pressor action of epinephrine. The doses required, however, are much larger than those which can be administered to human beings. Otto [7] has further demonstrated that even larger doses are necessary to paralyze the cardiac sympathetic innervation. In three cases ventricular rhythm of a prefibrillation type was induced by the intravenous injection of 0.1 mg. of epinephrine hydrochloride. Ergotamine tartrate was administered in 1 mg. doses, in 1 instance intravenously and in 2 instances subcutaneously. After various intervals

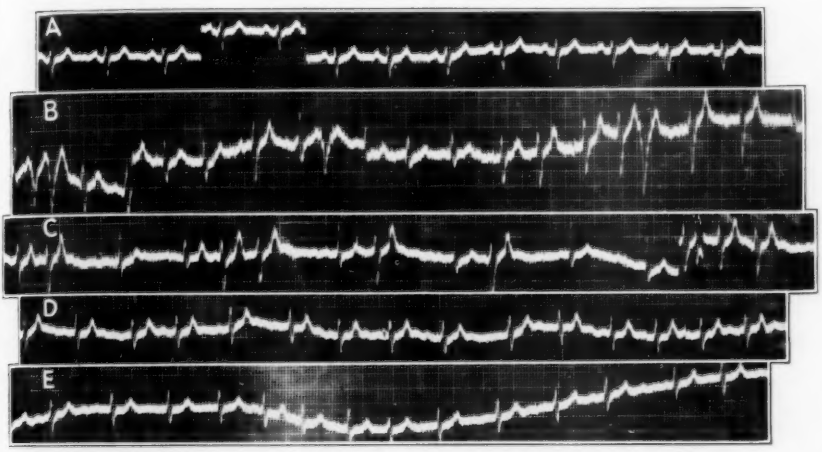

Fig. 3 (J. Q.).—Lead II. *A* was made before the injection of epinephrine; *B*, *C*, *D* and *E* were made one, two, three and four minutes, respectively, after the intravenous injection of 0.1 mg. of epinephrine. *B* and *C* consist almost entirely of ectopic beats from multiple ventricular foci (a prefibrillation rhythm).

epinephrine was again injected intravenously. The reactions were similar to those produced prior to the administration of ergotamine, indicating that ergotamine in doses suitable for man is ineffective in preventing a prefibrillation rhythm.

Potassium Salts.—There is experimental evidence that an excess of potassium ions in perfusion fluid prevents the formation of ectopic beats. Wiggers [15] and Hooker [16] found that potassium chloride is effec-

15. Wiggers, C. J.: Studies on Ventricular Fibrillation Caused by Electric Shock, Am. Heart J. **5**:346, 1930.

16. Hooker, D. R.: On the Recovery of the Heart in Electric Shock, J. Physiol. **91**:305, 1929.

tive in the prevention of the ventricular fibrillation produced by electric shock. Sampson and Anderson [17] have reported favorable results in the prevention of ventricular rhythm by the oral administration of potassium salts. In 2 cases in which epinephrine injected intravenously produced

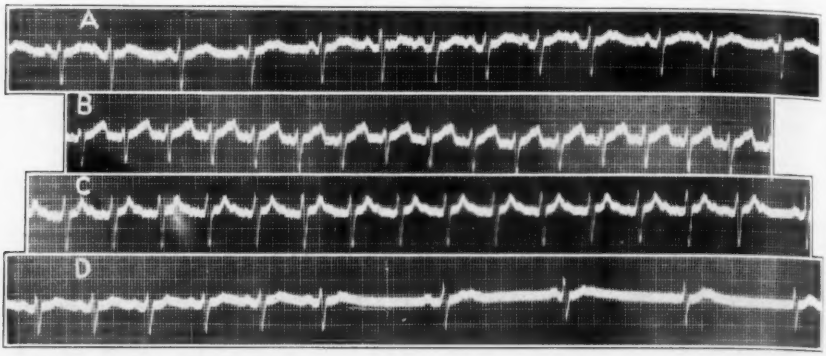

Fig. 4 (J. Q.).—Lead II, one hour after the administration of 2 Gm. of quinidine sulfate in divided doses. *A* was made before the intravenous injection of epinephrine was given; *B*, *C* and *D* were made one, two and four minutes, respectively, after the injection of 0.1 mg. of epinephrine. The ectopic ventricular beats are entirely eliminated.

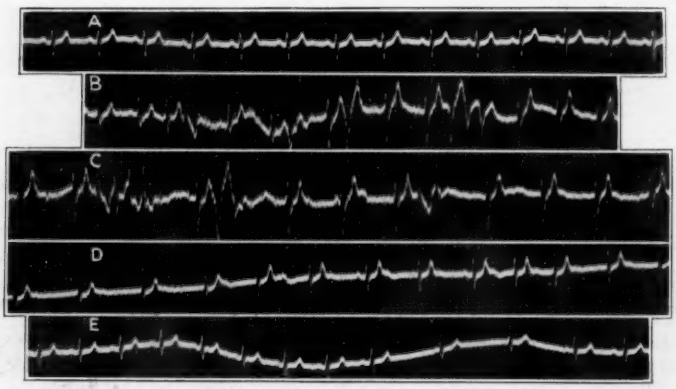

Fig. 5 (J. Q.).—Lead II, six days after the use of quinidine was discontinued. *A* was taken before epinephrine was given; *B*, *C*, *D* and *E* were taken one, two, three and four minutes, respectively, after 0.1 mg. of epinephrine hydrochloride was given. Ectopic ventricular beats from multiple foci are again induced.

17. Sampson, J. J., and Anderson, E. M.: The Treatment of Certain Cardiac Arrhythmias with Potassium Salts, J. A. M. A. **99**:2257 (Dec. 31) 1932.

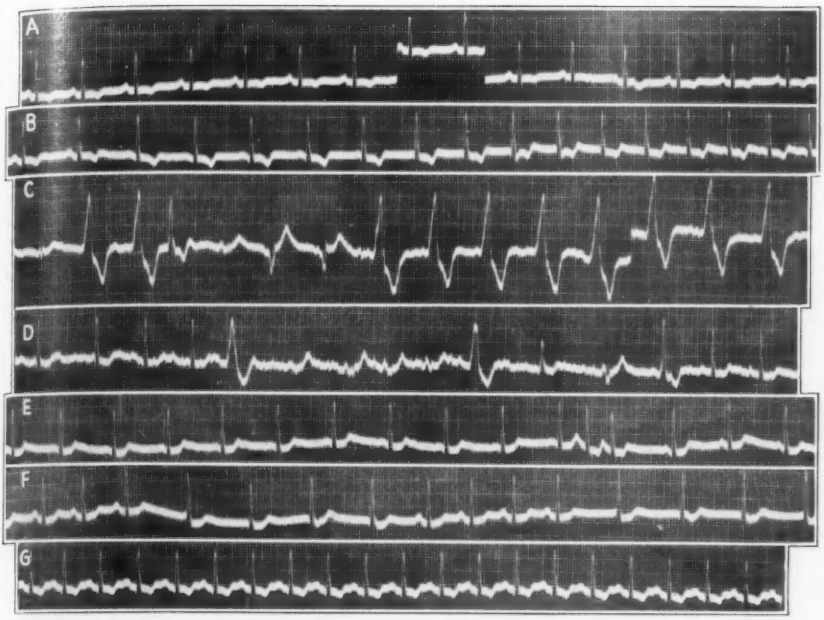

Fig. 6 (M. S.).—Lead II. *A* was taken before epinephrine was given; *B* was taken thirty seconds and *C*, *D*, *E*, *F* and *G* were taken at one minute intervals following the intravenous injection of 0.1 mg. of epinephrine hydrochloride. Note that all beats in strip *C* and many in *D* are ectopic ventricular in origin.

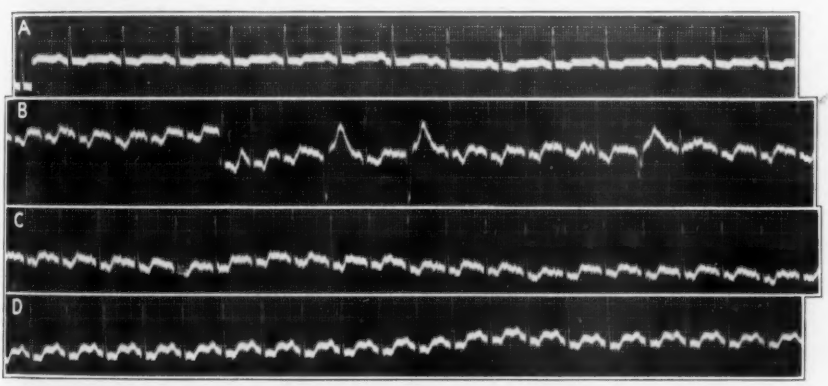

Fig. 7 (M.S.).—Lead II, one hour after the administration of 1 Gm. of quinidine sulfate. *A* was taken before epinephrine was given; *B*, *C* and *D* were taken one, three and five minutes, respectively, after the intravenous injection of 0.1 mg. of epinephrine hydrochloride. Note the modification of the reaction as compared with that shown in figure 6. Only three ectopic ventricular beats were induced over a period of five minutes.

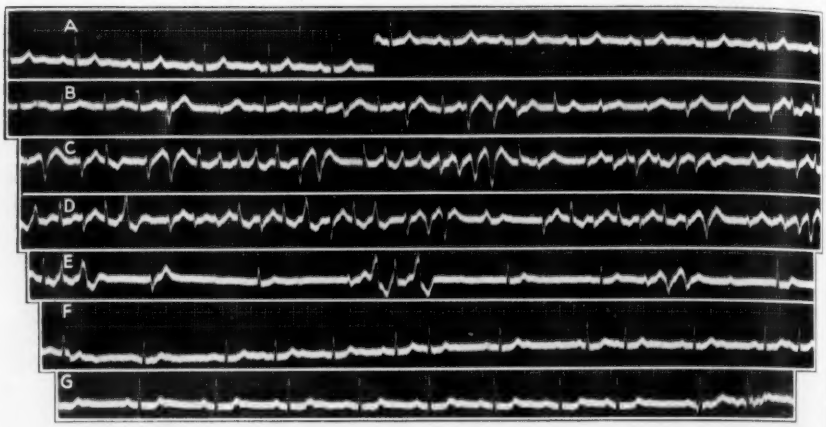

Fig. 8 (G. S.).—Lead II. *A* was taken before epinephrine was given. The lower strips were taken at one minute intervals following the intravenous injection of 0.1 mg. of epinephrine hydrochloride. The epinephrine induced ectopic ventricular beats from multiple foci at a rapid rate and in groups. This is most marked in *C* and *D*.

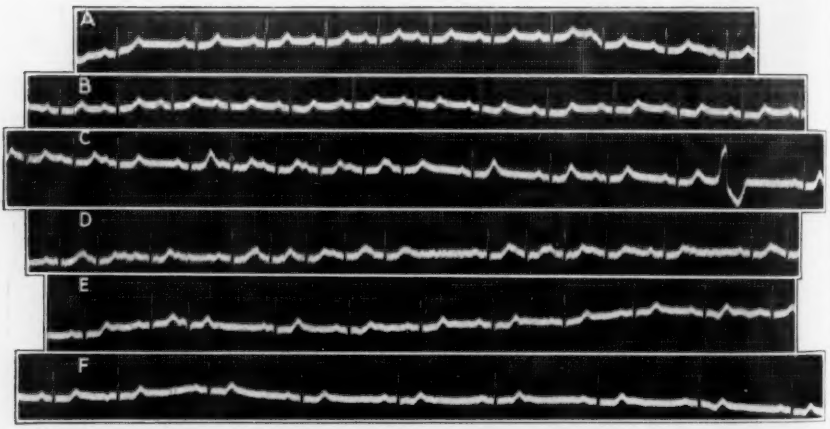

Fig. 9 (G. S.).—Lead II, one hour after the administration of 2 Gm. of quinidine sulfate in divided doses. *A* was taken before epinephrine was given; *B, C, D, E* and *F* were taken at one minute intervals following the intravenous administration of 0.1 mg. of epinephrine hydrochloride. Only one ectopic ventricular beat was induced (strip *C*). This reaction should be compared with that shown in figure 8.

a prefibrillation rhythm, potassium acetate was administered orally in daily doses of 6 and 8 Gm. for four and five days, respectively. After this period the intravenous injection of epinephrine was repeated, and the reactions were similar to those induced prior to the administration of potassium acetate. These studies are insufficient to establish definitely the status of potassium salts. Larger doses may be necessary, since Sampson and Anderson found that some patients reacted only to large doses—up to 16 Gm.

Acetyl-Beta-Methylcholine.—The administration of this substance produces the effects of stimulation of the vagus nerve, which theoretically may counteract the action of sympathetic stimulation on the ventricles. Nahum and Hoff [8] reported that ventricular fibrillation in cases of acute benzene poisoning can be prevented by the administration of

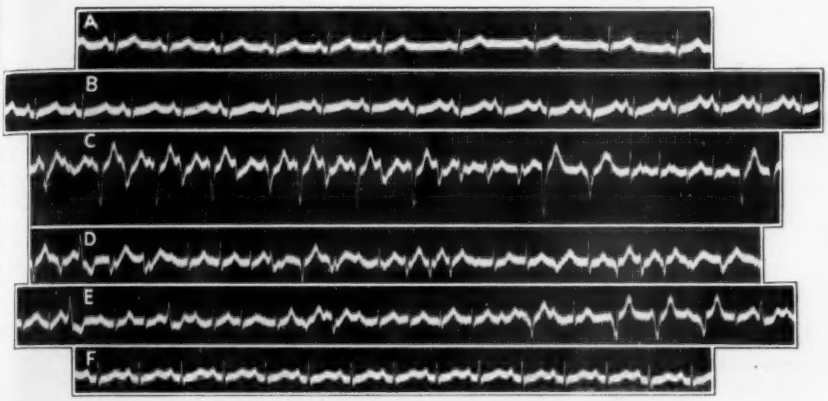

Fig. 10 (M. D.).—Lead II; *A*, before the injection of epinephrine. *B* was taken thirty seconds afterward. The lower strips were taken at one minute intervals following the injection. Note the ectopic ventricular beats from multiple foci in strips *C*, *D* and *E*.

acetyl-beta-methylcholine. In the present study the reaction to 0.1 mg. of epinephrine was observed before and after a subcutaneous injection of acetyl-beta-methylcholine chloride. The second dose of epinephrine was administered five minutes after the injection of 20 mg. of acetyl-beta-methylcholine chloride. In 5 of 6 cases the ventricular rhythm induced by epinephrine was almost completely eliminated (figs. 11 and 12). In 1 instance the effect of epinephrine was not modified to any degree.

Sodium Amytal.—Seevers and Meek [18] produced ventricular rhythm in dogs by the intravenous injection of ephedrine. It was found that the

18. Seevers, M. H., and Meek, W. J.: Barbiturate Protection from Cardiac Irregularities Induced by Ephedrine, J. Pharmacol. & Exper. Therap. **48**:286, 1933.

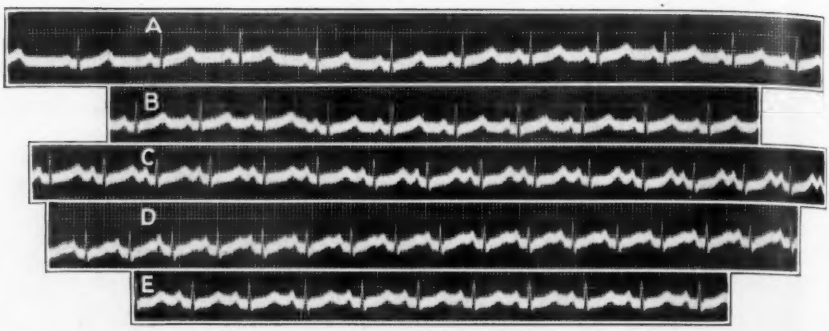

Fig. 11 (M. D.).—Lead II; *A*, before the administration of acetyl-beta-methylcholine. *B* was taken two minutes after the subcutaneous injection of acetyl-beta-methylcholine chloride, 20 mg. *C* was taken two minutes after the intravenous injection of 0.1 mg. of epinephrine hydrochloride, which was administered six minutes after the acetyl-beta-methylcholine. *D* and *E* were taken four and five minutes, respectively, after epinephrine was given. Note the absence of ectopic ventricular beats.

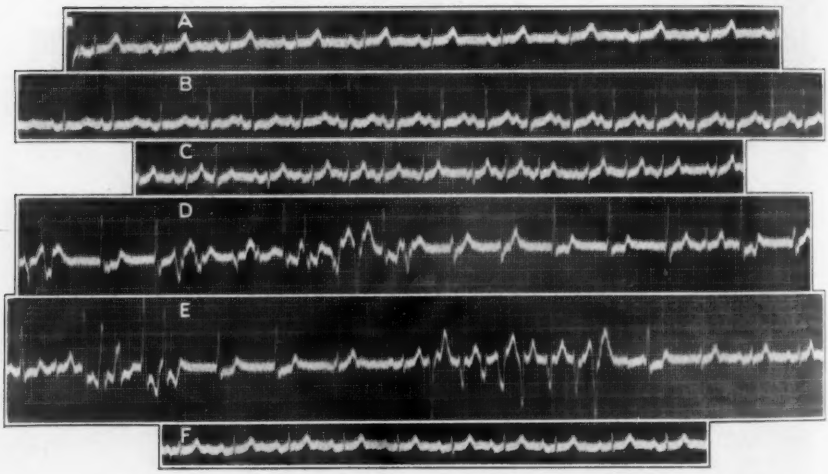

Fig. 12 (S. D.).—Lead II. *A* was taken before epinephrine was given. The lower strips were taken thirty seconds, one, two, three and five minutes, respectively, after the intravenous injection of 0.1 mg. of epinephrine hydrochloride. *D* and *E* show groups of rapid ectopic ventricular beats.

various barbiturates afforded considerable protection against these irregularities. The doses used, however, were larger than those which can be administered to man. In 1 patient the intravenous injection of sodium amytal, 0.25 Gm., resulted in sound sleep. The administration of epinephrine at this time induced ectopic ventricular beats similar to those of the control record.

Action of Quinidine on the Vagus Nerve.—There is a further action of quinidine which is of practical interest in this connection. Quinidine acts directly on the myocardium and is a powerful cardiac depressant. The activity of the sinus node is definitely depressed. Although the evidence is against Allbutt's conception of death by vagus inhibition of the heart, the possibility that this mechanism may operate in some cases

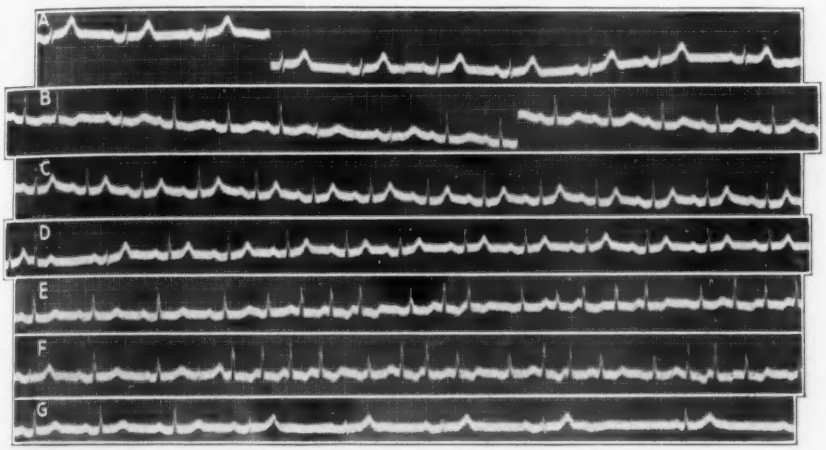

Fig. 13 (S. D.).—Lead II. *A* is the control record taken seven minutes after the subcutaneous injection of 20 mg. of acetyl-beta-methylcholine chloride. At this time epinephrine hydrochloride, 0.1 mg., was injected intravenously, and the lower strips form part of a continuous record taken over a period of five minutes after the injection of epinephrine hydrochloride. Compare with figure 12 and note that the acetyl-beta-methylcholine prevented the development of ectopic ventricular beats.

cannot be absolutely excluded. From this standpoint quinidine may be considered harmful, for the action of a sensitive vagus nerve on a sinus node depressed by quinidine tends to favor permanent cardiac standstill. However, Lewis and his associates [19] have demonstrated in dogs that in addition to its direct cardiac action, quinidine possesses also a powerful

19. Lewis, T.; Drury, A. N.; Iliescu, C. C., and Wedd, A. M.: Observations Relating to the Action of Quinidine upon the Dog's Heart, Heart **9**:55, 1921.

vagoparetic effect. Dale [20] showed in cats that the effect of the vagus nerve on the sinus node was completely eliminated by quinidine. In a previous study [21] a similar action was demonstrated in man. Six subjects were selected in whom pressure over the carotid sinus produced an intense vagal effect on the sinus node, with prolonged cardiac standstill (fig. 13). After the administration of quinidine sulfate, from 1.8 to 2.2 Gm. in divided doses, the effect of the reflex stimulation of the vagus nerve was so reduced that only slight slowing of the heart was obtained. Thus quinidine by its direct action on the ventricular muscle lessens the tendency to ventricular fibrillation and by its vagoparetic effect tends to prevent vagal inhibition of the heart.

PRACTICAL APPLICATIONS

Cardiac Standstill.—Studies on the action of drugs on induced cardiac standstill demonstrate that the various sympathomimetic amines are applicable in the treatment of ventricular standstill such as occurs

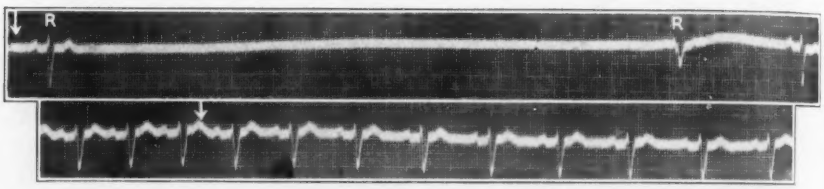

Fig. 14 (J. Q.).—The upper strip shows cardiac standstill of eleven seconds induced by pressure on the right carotid sinus (arrow). The lower strip was taken after the administration of quinidine sulfate, 2.2 Gm. Pressure on the carotid sinus produced only slight vagus stimulation, slowing of the heart rate from 80 to 58 per minute.

in cases of heart block. Substances unrelated to epinephrine in chemical structure and in physiologic action will almost certainly be ineffective. Epinephrine is the most active compound and should be used when syncopal attacks are frequent. Experiments on the duration of action by the present method indicate that a subcutaneous injection of 1 mg. every three hours will raise the ventricular rhythmicity so that standstill will be prevented. Ephedrine is the most active compound which is effective on oral administration. There is a great variation in the degree to which the human ventricles react to this drug. In some instances 25 mg. injected intravenously increased the ventricular rhythmicity, while in other cases 100 mg. was required. Thus, if an effect is not

20. Dale, H. H.: Note on the Reversal of Vagus Action by Quinidine as Seen in the Heart of the Cat, Heart **9**:87, 1921.

21. Nathanson, M. H.: Modification of Vagus Inhibition of the Heart by Quinidine, Proc. Soc. Exper. Biol. & Med. **31**:1234, 1934.

obtained with the usual oral dose, the amount should be increased up to 150 mg. If this is ineffective, it will be necessary to resort to epinephrine by subcutaneous injection.

Ventricular Fibrillation.—The present studies show that the action of epinephrine on the ventricular myocardium may be modified and that an induced ectopic ventricular rhythm may be prevented by drugs. This provides a basis for the prophylactic treatment of patients who are liable to sudden death. Whether protection is actually afforded in practice and the degree of this protection cannot be evaluated at present. Morawitz and Hochrein [22] used quinidine empirically for the prevention of acute cardiac death. They concluded from a comparison of a series of treated and untreated patients that quinidine lessened the incidence of sudden death. In the past two years quinidine sulfate has been administered as follows: (1) for six or eight weeks following coronary occlusion and (2) in cases of angina pectoris in which there is evidence of hyperirritability of the ventricles, i. e., frequent ventricular extrasystoles. The dose has usually been 0.4 Gm. three times a day. The number of patients observed is too small for the drawing of any final conclusions as to the efficiency of the drug in the prevention of ventricular fibrillation. No harmful effects were observed. This is mentioned because instances of transient ventricular fibrillation have been reported in patients under quinidine therapy.[23] It cannot be assumed definitely that quinidine was responsible for these attacks, as they may have developed spontaneously. Cases have been reported also in which quinidine seemed to prevent attacks of transient ventricular fibrillation.[24] Unfortunately transient ventricular fibrillation is of infrequent occurrence, and there is little opportunity to study the action of drugs in the prevention of this arrhythmia in clinical cases. It seems, however, that the strong evidence of the relationship of epinephrine to ventricular fibrillation and the present studies demonstrating the antagonism of quinidine on the action of epinephrine on the ventricular myocardium justify the use of this drug and a study of the results in a series of suitable cases. Further studies are being carried out with acetyl-beta-methylcholine, and it is possible that this drug may be of practical value as a prophylactic measure in cases of ventricular fibrillation.

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22. Morawitz, P., and Hochrein, M.: Zur Verhütung des akuten Herztodes, München. med. Wchnschr. **76**:1075, 1929.

23. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, Am. Heart J. **4**:559, 1929. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Therapy, Heart **9**:269, 1921.

24. Escamilla, R. F.: Report of a Case of Paroxysmal Ventricular Fibrillation in Relation to Quinidine Therapy, Am. Heart J. **8**:850, 1933. Dock.[12]

In addition to the use of drugs, there is a possibility that the factors which dispose the ventricles to fibrillation may be modified in other ways. It is clear that the use of all sympathomimetic drugs, such as epinephrine and ephedrine, is contraindicated, since they stimulate the endings of the sympathetic nerves. Cannon has shown that emotional excitement causes a special discharge of epinephrine, with increased activity of the sympathetic system. It is a familiar fact that emotional excitement is a potent exciting factor of the anginal attack. The relationship between the cardiac accelerator innervation and ventricular fibrillation suggests that nervous and emotional stimuli may tend to induce the mechanism which causes the fatal syncope. Therefore, a most important indication in the prevention of sudden death is therapy directed at the nervous and emotional status of the patient. In addition to the use of quinidine, the application of methods which tend to lessen the activity of the sympathetic nervous system appears to be a rational therapeutic procedure.

SUMMARY

Structural changes in the heart are usually inadequate to explain either temporary or fatal cardiac syncope.

There are two physiologic mechanisms in the heart which may cause sudden cessation of the circulation: (1) cardiac standstill and (2) ventricular fibrillation. In the present study it was possible to manipulate the human cardiac mechanism (1) mechanically, producing cardiac standstill by reflex vagus stimulation, and (2) chemically, inducing a prefibrillation state in the ventricles by sympathetic stimulation with epinephrine administered intravenously. It has been demonstrated that both of these physiologic states may be definitely modified by drugs.

Drugs of the epinephrine series in proper dosage will prevent cardiac standstill.

Prefibrillation rhythm may be prevented by the use of quinidine or of acetyl-beta-methylcholine.

Protection of the sympathetic nervous mechanism by general measures is indicated.

These studies suggest an approach by drug therapy and by general measures toward the prevention of cardiac syncope and sudden death.

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EFFECT OF PROLONGED DIETARY RESTRICTION ON PATIENTS WITH CARDIAC FAILURE

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In June 1933 there came to our attention a 14 year old girl who presented features suggesting hypopituitarism, possibly due to prolonged undernutrition. One of the striking findings was sinus bradycardia of 34 per minute. From personal inquiry and a survey of the literature it appeared that cardiologists in general are unaware that prolonged undernutrition may produce such marked bradycardia. Further studies on this patient of various cardiovascular features, such as the blood flow and the response to exercise, indicated that the bradycardia was associated with a favorable functional state of the circulatory system.

That marked bradycardia may be the result simply of prolonged undernutrition was first observed by Benedict and his associates,[1] who also showed that many of the other features which we observed in our patient, such as a low basal metabolic rate (—37 per cent), low blood pressure (80 systolic and 60 diastolic), a diminished intake of fluid (as low as 640 cc. a day) and a small output of urine (as low as 270 cc. a day), likewise might follow a low food intake, over a prolonged period. Since all these conditions seem eminently desirable in patients with cardiac weakness and since they evidently could be produced simply by prolonged dietary restriction, we began the study of the effect of such dietary management on patients with cardiac disease.

Dietary restriction as a treatment for heart disease is by no means new; empirically it has been employed for many years. As an example may be mentioned the Karell diet, which is essentially a starvation diet and has been widely used purely on an empirical basis for about

This study was made possible by grants from the Bingham Associates Fund and the Ella Sachs Plotz Foundation.

From the Medical Clinic of the Boston Dispensary and the Department of Medicine, Tufts College Medical School.

1. Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: Human Vitality and Efficiency Under Prolonged Restricted Diet, Washington, D. C., Carnegie Institution of Washington, 1919.

seventy years. Dietary restriction has been a more or less important feature of the management of cardiac failure in the hands of many physicians. Thus, J. H. Pratt, under whom the present investigation was carried out, has for thirty years recommended a restricted diet in association with absolute rest in bed, his procedure being to place the patient on the Karell diet for several days and then slowly increase the amount of food so that actually for two or three weeks the patient received a meager diet. It was our purpose in the present research to determine what, if any, might be the specific objective and measurable advantages of prolonged dietary restriction and whether such a procedure is desirable in fact as well as in theory.

The earliest results of this type of treatment were reported as encouraging.[2] A summary of our observations up to the beginning of 1935 has been presented elsewhere.[3] Also we have reported our observations on two patients with angina pectoris who were submitted to prolonged undernutrition.[4] Despite what was considered a sufficient loss of weight in both patients and a significant drop in the basal metabolism in one of the patients, there was no objective evidence that the undernutrition was of particular benefit.[4a]

PROCEDURE AND MATERIAL FOR PRESENT STUDY

The present report deals with observations on six white patients, four men and two women, all but one showing signs of severe congestive heart failure when the studies were begun. The one patient who did not show signs of heart failure had syphilitic aortitis with aortic insufficiency, marked cardiac enlargement and angina pectoris and presented a history of recent cardiac failure. Of the other five patients, three had senile heart disease, one had concretio cordis and one had

2. Proger, S. H.: Boston Dispensary Staff Meeting, March 1934.

3. Proger, S. H., and Magendantz, H.: The Effect of Prolonged Dietary Restriction on Patients with Cardiac Weakness, J. Clin. Investigation **14**:720, 1935.

4. Proger, S. H.; Minnich, W. R., and Magendantz, H.: The Circulatory Response to Exercise in Patients with Angina Pectoris, Am. Heart J. **10**:511, 1935.

4a. Master, Jaffe and Dack, apparently with the view chiefly of lowering the level of oxygen consumption, have employed reduction of food in the treatment of patients with disease of the coronary arteries (particularly thrombosis). Their observations form the basis of several recent reports (Master, A. M.: Coronary Artery Thrombosis, with Treatment by Prolonged Rest in Bed and Low Calory Diet: Improved Prognosis, J. A. M. A. **105**:337 [Aug. 3] 1935. Master, A. M.; Jaffe, H. L., and Dack, S.: Low Basal Metabolic Rates Obtained by Low Calorie Diets in Coronary Artery Disease, Proc. Soc. Exper. Biol. & Med. **32**:779, 1935; The Basal Metabolic Rate in a Patient with Coronary Artery Thrombosis When Placed on an Eight Hundred Calorie Diet, J. Mt. Sinai Hosp. **1**:263, 1935; Undernutrition in the Treatment of Coronary Artery Disease [Particularly Thrombosis]: Effect on the Basal Metabolism and Circulation, J. Clin. Investigation **15**:353, 1936). Our work, done without knowledge of theirs and concerned with heart failure rather than disease of the coronary arteries, revealed many similar results.

rheumatic heart disease with mitral stenosis and regurgitation. One of the two women patients was definitely obese before treatment was instituted. The other patients were of average or slightly below average weight. Observations were made of the arterial and venous blood pressures, cardiac rate, velocity of blood flow, cardiac output, respiratory rate, pulmonary ventilation, oxygen consumption, basal metabolic rate, vital capacity, response to exercise, muscle strength, output of urine, intake of fluid, intake and output of nitrogen, output of sodium chloride, erythrocyte and hemoglobin content of the blood and the blood sugar content. In addition, in one case repeated measurements were made of the serum protein, blood cholesterol and blood calcium. In this case also electrocardiograms and roentgenograms were repeatedly made.

Each patient was first treated with absolute rest in bed, morphine and other sedatives as required, the intake of food and fluid usually being unrestricted. After a sufficient period of time under this regimen had elapsed so that the patient's condition seemed stationary and a fairly good control period was established, digitalis was added to the treatment, all other conditions remaining fixed. Observations could then be made on the isolated effect of digitalis. When another stationary period was reached with digitalis added to the treatment and observations had been made during a sufficiently long period, dietary restriction was instituted, all other conditions again remaining fixed. In this manner, it seemed to us that we were able to separate those changes in the cardiovascular state which were due to the dietary restriction from the beneficial effects of rest in bed, sedatives and digitalis. At first a diet calorically equivalent to the Karell diet[5] was given, and the intake of fluid and salt was unrestricted. As previously noted, the Karell diet has been recognized for many years as being beneficial in the presence of heart failure. Whether this favorable effect is due to the restriction of calories, fluid protein or salt is not known, the diet being limited in all respects. It was our purpose to limit only the calories, so as to determine the influence of this factor alone. Since the diet as we employed it contained only 356 calories,[6] there was obviously a deficiency of protein (carbohydrate, 48 Gm.; protein, 32 Gm., and fat, 4 Gm.). However, a negative protein balance is a necessary accompaniment of rapid loss of weight in a person of normal size.[7] In fact, it may be that many of the changes which we observed were due to the loss of protein, though convincing evidence points contrariwise.[8]

After one or two weeks the diet was increased to contain about 600 calories (carbohydrate, 80 Gm.; protein, 43 Gm., and fat, 13 Gm.), and the patient was kept on this diet until the desired loss of weight (about 10 per cent of the body weight) had been obtained, after which the caloric intake was increased sufficiently to maintain a constant weight at the new level. The required intake for this purpose with the patient in bed was from 800 to 1,000 calories. On discharge the patient was allowed 1,200 calories (carbohydrate, 121 Gm.; protein, 63 Gm., and fat, 53 Gm.). This, though theoretically insufficient, was found to be adequate for maintenance of the low level of weight while there was moderate activity, because patients, particularly the type with which we were dealing, generally are not absolutely rigid in their adherence to a diet.

5. Karell, P.: De la cure de lait, Arch. gén. de méd. **2**:513, 1866.

6. Miss Helen Finkelstein, of the Food Clinic, gave valuable assistance in the dietary management in these cases.

7. Jansen, W. H.: Untersuchungen über Stickstoffbilanz bei kalorienarmer Ernährung, Deutsches Arch. f. klin. Med. **124**:1, 1917.

8. Lusk, G.: The Physiological Effect of Undernutrition, Physiol. Rev. **1**:523, 1921.

TABLE 1.—*The Sample Diets and Menus of the Different Caloric Levels* *

Food	Total	Carbohydrate	Protein	Fat	Calcium	Phosphorus	Iron	Sample Menu for One Day: Morning	Noon	Night
Diet of 356 Calories								⅔ ounce cottage cheese ½ slice bread ½ glass skimmed milk Coffee	1½ ounces meat or fish 1 serving vegetable ¼ glass skimmed milk 1 serving fruit Tea	½ ounce cottage cheese 1 serving vegetable ½ slice bread ¼ glass skimmed milk Tea
Skimmed milk	240	12	8	1	0.293	0.230	0.0006			
Meat, fish or chicken	45	..	12	3	0.006	0.112	0.0015			
Cottage cheese	35	1	7	..	0.088	0.285	.....			
Bread, whole grain	30	16	3	..	0.015	0.065	0.0007			
Vegetables, 5 per cent.	200	8	2	..	0.022	0.052	0.0008			
Fruit, 10 per cent	100	11	..	..	0.045	0.021	0.0005			
Totals		48	32	4	0.469	0.765	0.0041			
Diet of 609 Calories								1 serving fruit ½ ounce cottage cheese ½ slice bread ½ glass skimmed milk Coffee	2 ounces meat or fish 1 serving vegetable ½ ounce cottage cheese ½ slice bread ¼ glass milk 1 serving fruit Tea	1 egg or 1 ounce cheese 1 serving vegetable ½ ounce cottage cheese ½ slice bread ¼ glass milk 1 serving fruit Tea
Skimmed milk	240	12	8	1	0.293	0.230	0.0006			
Meat, fish or chicken	60	..	14	7	0.008	0.150	0.0020			
Egg	(1)	..	6	5	0.033	0.090	0.0015			
Cottage cheese	45	2	9	..	0.112	0.366	.....			
Bread, whole grain	45	24	4	..	0.022	0.0982	0.0011			
Vegetables, 5 per cent.	200	8	2	..	0.022	0.052	0.0008			
Fruit, 10 per cent	300	33	..	..	0.135	0.063	0.0015			
Totals		80	43	13	0.625	1.0492	0.0075			
Diet of 800 Calories								1 serving fruit ½ ounce cottage cheese 1 slice bread ½ glass skimmed milk Coffee	3 ounces meat or fish 1½ servings vegetable ½ ounce cottage cheese 1 slice bread ¼ glass skimmed milk 1 serving fruit Tea	1 egg or 1 ounce cheese 1½ servings vegetable ½ ounce cottage cheese 1 slice bread ¼ glass skimmed milk 1 serving fruit Tea
Skimmed milk	240	12	8	1	0.293	0.230	0.0006			
Meat, fish or chicken	90	..	22	10	0.012	0.225	0.0030			
Egg	(1)	..	6	5	0.033	0.090	0.0015			
Cottage cheese	45	2	9	..	0.112	0.366	.....			
Bread, whole grain	90	48	9	..	0.045	0.196	0.0021			
Vegetables, 5 per cent.	300	12	3	..	0.033	0.078	0.0012			
Fruit, 10 per cent	300	33	..	..	0.135	0.063	0.0015			
Totals		107	57	16	0.663	1.248	0.0099			
Diet of 1,095 Calories								1 serving fruit 1 teaspoon butter 1 slice bread ½ glass milk Coffee	4 ounces meat or fish 1½ servings vegetable 1 teaspoon butter 1 slice bread ½ glass milk 1 serving fruit Tea	1 egg or 1 ounce cheese 1½ servings vegetable 1 teaspoon butter 1 slice bread ½ glass milk 1 serving fruit Tea
Milk	360	18	12	15	0.432	0.334	0.0009			
Meat, fish or chicken	120	..	27	14	0.016	0.300	0.0040			
Egg	(1)	..	6	5	0.033	0.090	0.0015			
Bread, whole grain	90	48	9	..	0.045	0.196	0.0021			
Vegetables, 5 per cent.	300	12	3	..	0.033	0.078	0.0012			
Fruit, 10 per cent	300	33	..	..	0.135	0.063	0.0015			
Butter	15	..	..	13	0.002	0.003	.....			
Totals		111	57	47	0.696	1.064	0.0112			
Diet of 1,200 Calories								1 serving fruit 1 teaspoon butter 1 slice bread ½ glass milk Coffee	4 ounces meat or fish 2 servings vegetables 1 teaspoon butter 1 slice bread ½ glass milk 1 serving fruit Tea	1 egg or 1 ounce cheese 2 servings vegetables 1 teaspoon butter 1 slice bread 1 glass milk 1 serving fruit Tea
Milk	480	24	16	20	0.576	0.445	0.0012			
Meat, fish or chicken	120	..	27	14	0.016	0.300	0.0040			
Egg	(1)	..	6	5	0.033	0.090	0.0015			
Bread, whole grain	90	48	9	..	0.045	0.196	0.0021			
Vegetables, 5 per cent.	400	16	4	..	0.044	0.104	0.0016			
Fruit, 10 per cent	300	33	..	..	0.135	0.063	0.0015			
Butter	15	..	..	13	0.002	0.003	.....			
Totals		121	62	52	0.851	1.201	0.0119			

* Normal mineral requirement for an adult: calcium, 0.68 Gm.; phosphorus, 1.32 Gm.; iron, 0.015 Gm., per day.

While in the hospital each patient was kept at absolute rest in bed, being allowed bathroom privileges only during the latter part of his stay. The patient was taken to the laboratory in the morning, where all tests were made under basal conditions. During these tests the patient was in a semirecumbent position. Observations were made of the basal metabolic rate both with the Benedict-Roth and with the Tissot spirometer. The basal metabolic rate was calculated according to the Aub-Du Bois standards. The observations during exercise were made in the afternoon, from three to four hours after the noon meal. Exercise consisted of pedaling on a stationary bicycle of the Prony-brake type at a fixed rate against a constant pull. During exercise observations were made on the pulse rate, respiratory rate and respiratory minute volume and in one case on the oxygen consumption.

The acetylene method of Grollman [9] was used to measure the cardiac output and the decholin method of Winternitz, Deutsch and Brüll [10] was used for measuring the velocity of the blood flow. At the time the measurements of the cardiac output were made the degree of pulmonary congestion was not so great as to interfere with the obtaining of samples of true alveolar air.[11] In three of the cases repeated measurements were considered unsatisfactory owing to a lack of cooperation. The venous pressure was measured by a modified Moritz-Tabora method.[12] The size of the heart was traced from roentgenograms taken at a distance of 2 meters, with the patient standing. The area was measured with a planimeter, as suggested by Levy.[13] The heart rate, which was counted for a full minute at the apex and the blood pressure, which was measured also by auscultation, were taken twice within a period of about five minutes. The lower values are recorded.

The various chemical measurements were made according to the methods of Hagedorn and Jensen [14] (blood sugar), Clark and Collip [15] (serum calcium), Howe [16] (blood sugar) and Folin and Denis [17] (urinary nitrogen) and by Oser

9. Grollman, A.: The Determination of the Cardiac Output of Man by the Use of Acetylene, Am. J. Physiol. **88**:432, 1929.

10. Winternitz, M.; Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion, Med. Klin. **27**:986, 1931.

11. Grollman, A.; Proger, S. H., and Dennig, H.: Zur Bestimmung des Minutenvolumens mit der Azetylenmethode bei Arbeit, bei normalen und kranken Menschen, Arch. f. exper. Path. u. Pharmakol. **162**:463, 1931.

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and Karr's[18] modification of the method of Myers and Wardell[19] (blood cholesterol).

REPORT OF CASES

CASE 1.—G. W., a man aged 68, had had increasing dyspnea on exertion for three years. In the past two years there had also been slight substernal pain on exertion, which was relieved by rest. No pain had been noted in the few months before the patient's admission to the hospital. In the year before the studies were begun he was admitted three times to the Boston City Hospital with congestive heart failure. Examination showed slight orthopnea, cyanosis, considerable cardiac enlargement, regular action of the heart, a heart rate of 80, hepatic engorgement (the edge of the liver was 4 cm. below the costal margin in the right midclavicular line) and moderate pretibial pitting edema. Roentgenograms confirmed the diagnosis of a markedly dilated heart. An electrocardiogram showed partial auriculoventricular block (P R interval, 0.25 second) and left bundle branch block. There was considerable improvement after rest in bed and digitalis therapy. The subsequent changes are noted in table 2.

CASE 2.—M. A., a man aged 48, as long as nine years before his admission to the hospital had noted some nocturnal edema about the ankles. The condition had gradually become more noticeable. In the past four or five years there had been increasing dyspnea on exertion. In the past year there had been orthopnea, which in the few weeks before the patient's admission to the hospital had become extreme, being accompanied by a constant nonproductive cough. Examination showed moderate orthopnea, slight cardiac enlargement and rapid auricular fibrillation. The pulse rate was 114, with a deficit of 20. The blood pressure was 130 systolic and 88 diastolic. There were moist râles at the bases of both lungs. The edge of the liver was felt 8 cm. below the costal margin, and there was moderate pretibial pitting edema. Roentgenograms showed evidence of a calcified pericardium (etiology not determined after careful inquiry), slight cardiac enlargement and bilateral slight pleural effusion. An electrocardiogram showed only low voltage and auricular fibrillation. There was only slight improvement until digitalis was given on the tenth day, after which the orthopnea, edema and pulmonary congestion disappeared. The size of the liver did not diminish considerably, and it was still at least 4 cm. below the costal margin when the patient was discharged after dietary restriction. The changes following dietary restriction are recorded in table 2.

CASE 3.—L. McM., a woman aged 50, was admitted to the hospital only two weeks after the sudden onset of dyspnea, epigastric distress, palpitation and general weakness. In the two weeks before her admission to the hospital the symptoms had become progressively more severe. During the week preceding the onset of symptoms she had performed an unusually great amount of physical work. There had been no infection. There was no previous history of rheumatic infection. Examination showed moderate orthopnea, slight cyanosis, considerable cardiac enlargement to the right and left, a mitral diastolic murmur with a booming first sound, rapid auricular fibrillation (120) with a moderate pulse deficit, moist râles at the bases of both lungs with evidence of pleural effusion on the right, hepato-

18. Oser, B. L., and Karr, W. G.: The Lipoid Partition in Blood in Health and in Disease, Arch. Int. Med. **36**:507 (Oct.) 1925.

19. Myers, V. C., and Wardell, E. L.: The Colorimetric Estimation of Cholesterol in Blood, with a Note on the Estimation of Coprosterol in Feces, J. Biol. Chem. **36**:147, 1918.

TABLE 2.—*Data on the Changes Noted Following Dietary Restriction* *

Patient	Sex	Age, Years	Height, Cm.	Weight, Kg.		Standard Average Weight, Kg.	Surface Area, Sq. Cm.		Heart Rate per Minute		Blood Pressure				Velocity of Blood Flow, Seconds		Vital Capacity, Cc.		Respiratory Rate per Minute		Respiratory Minute Volume, Liters		Basal Metabolic Rate, Percentage		Oxygen Consumption, Cc. per Min.		Decrease in Oxygen Consumption, Percentage	Arteriovenous Oxygen Difference, Cc. per Liter		Cardiac Output, Liters per Min.		Cardiac Output per Sq.M. Surface Area, Liters per Min.		Stroke Output, Cc. per Beat	
											Before		After																						
				Before	After		Before	After	Before	After	Systolic	Diastolic	Systolic	Diastolic	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After		Before	After	Before	After	Before	After	Before	After
M. A.	M	48	165	69.0	50.0	64	1.75	1.63	73	50	110	70	100	60	22	23	3,350	3,725	18	13	6.5	4.9	— 7	—14	211	176	17	61	56	4.1	3.7	2.3	2.3	56	74
G. W.	M	68	165	64.8	54.0	68	1.70	1.57	72	59	126	86	110	70	27	25	2,450	2,900	12	9	5.9	5.3	+ 4	— 6	217	180	16	63	66	3.4	2.8	2.0	1.8	47	47
M. W.	M	60	163	64.8	58.4	66	1.69	1.61	59	45	140	42	140	36	30	33	3,100	3,550	17	13	8.4	5.9	+31	+ 2	276	205	26	..	..	...	...	...	...	..	..
F. C.	M	67	171	69.7	62.2	71	1.80	1.72	61	46	174	87	154	74	29	24	3,300	4,050	12	9	6.9	4.9	+ 5	—17	231	175	24	57	47	4.3	3.7	2.3	2.2	70	80
Average		61	166	67.1	58.4	..	1.74	1.63	66	50	138	71	126	60	27	26	3,050	3,550	15	11	6.9	5.3	+ 8	— 9	234	184	21	60	56	3.9	3.3	2.2	2.1	58	67
McM.	F	50	140	54.5	49.3	56	1.40	1.34	74	73	130	74	128	72	24	23	2,150	2,400	22	20	6.7	6.0	— 9	— 8	175	170	3	..	..	...	...	...	...	..	..
C. M.	F	57	148	67.3	58.8	61.5	1.60	1.51	81	70	150	86	120	74	40	35	800	1,200	20	17	7.3	5.7	+16	+11	234	200	14	..	..	...	...	...	...	..	..

* The averages given are for the four cases in which the changes were most striking.

megaly (the edge of the liver being 2 cm. below the costal margin) and slight pretibial pitting edema. There were no signs of hyperthyroidism. She responded well to thoracentesis, rest in bed with sedatives and digitalis, the further effect from dietary restriction being slight (table 2).

CASE 4.—C. M., a woman aged 57, had her first period of congestive heart failure two years before her admission to the hospital. After satisfactory treatment at that time she was comfortable with moderate restriction of activities until two months before her admission to the hospital, since when there had been increasing dyspnea on exertion, coughing and increasing edema of the lower extremities. Examination showed moderate obesity, orthopnea, marked cyanosis, marked pitting edema of the lower extremities and extending up to the lower part of the back, considerable cardiac enlargement to the right and left, a loud, rough apical systolic murmur, an accentunated second pulmonic sound, rapid auricular fibrillation, a blood pressure of 146 systolic and 90 diastolic, moist râles over the bases of both lungs and hepatomegaly, the edge of the liver being 5 cm. below the costal margin in the right midclavicular line. The clinical condition was moderately improved with rest in bed and sedatives followed by diuretics (salyrgan) and digitalis. There was definite though not striking further improvement with dietary restriction. After the effect had been noted of reducing the patient's weight from an overweight to a normal level, an attempt was made to study further the effect of reducing the weight to an underweight level. She refused to cooperate, however, and the weight was not reduced below the average level.

CASE 5.—M. W., a man aged 60, first noted abnormal dyspnea on exertion seven years before his admission to the hospital. At that time he was known to have syphilitic heart disease. For six years he had had substernal pain on exertion, particularly in the winter, which was regularly relieved by rest or glyceryl tri-nitrate therapy. He had irregular antisyphilitic treatment during this entire period. About six weeks before his admission to the hospital he had early signs of congestive heart failure which disappeared in a few weeks after rest in bed, sedatives and digitalis therapy. At the time of his admission to the hospital there were no signs of congestive heart failure. There were peripheral signs of aortic insufficiency. The heart was considerably enlarged to the left. There were diastolic and systolic blowing murmurs over the aortic area. The blood pressure was 180 systolic and 40 diastolic. This patient did not receive digitalis. The changes noted in table 2 followed a preliminary control period of simple rest in bed.

CASE 6.—F. C., a man aged 67, first noticed increasing dyspnea on exertion three months before his admission to the hospital. There was also increased coughing. Within two months marked orthopnea and probably some edema of the lower extremities were noted. The symptoms became progressively worse until the patient's admission to the hospital, when he was found to have marked orthopnea, Cheyne-Stokes respiration, alternating pulse, moderate cyanosis, pleural effusion on the right side, many medium-sized moist râles over the bases of both lungs, considerable cardiac enlargement, a cardiac rate of 100, a faint apical systolic blow, a blood pressure of 166 systolic and 110 diastolic, hepatomegaly (the edge of the liver was 5 cm. below the costal margin in the right midclavicular line) and slight pretibial pitting edema. He was irrational. Roentgenograms showed considerable cardiac enlargement with pleural effusion on the right. The electrocardiogram showed left axis deviation and inverted T waves in leads I and II. He did not seem to improve considerably with rest and morphine therapy alone. His condition was so serious that a Karell diet was given for four days. By

thoracentesis of the right side 1,000 cc. of fluid was removed. After thirteen days there was enough improvement so that studies could be begun. Subsequent data are given in figure 1.

RESULTS

In general the results were considered distinctly favorable in four of the six patients, the four men. In these the improvement in the cardiovascular state and the degree of diminution of the level of energy metabolism were out of proportion to the loss of weight. In the one obese woman whose weight was reduced from an overweight level to an average level [20] the corresponding changes were only proportional; thus, for example, with a loss of 18.5 per cent in body weight to an average level there was a corresponding fall in oxygen consumption of 17 per cent. In the other woman there were only slight functional changes which could be attributed to reduction of the weight to an underweight level.

In figure 1 are presented representative results in one of the four men. These may be taken as characteristic of what can be expected from the regimen as outlined. It will be seen that a loss of 16 pounds (7.3 Kg.), from 153 pounds (69.5 Kg.) to 137 pounds (62.2 Kg.), took place in about forty days. During the first thirty-six days of observation [21] the average daily intake of food was 2,320 calories; during the next nine days, 360 calories; during the next thirty-eight days, 600 calories, and thereafter, 800 calories. Digitalis was administered daily for fourteen days beginning with the twenty-third day, the total amount being 5 Gm. of the powdered leaf. This produced no subjective discomfort, though there were signs of delayed auriculoventricular conduction and depression of the ST interval in leads I and II. As may be seen in the figure, the effects directly attributable to digitalis were the slowing of the heart rate (in the presence of sinus rhythm) from about 72 to about 60 per minute, a moderate elevation of the systolic blood pressure (this effect only in this patient), an increase in the vital capacity of 600 cc. from the time when digitalis was given or 300 cc. from a previous high level, a slight decrease in the respiratory rate and in the respiratory minute volume and an increase in the cardiac output accompanied with a decrease in the arteriovenous oxygen difference.

20. Metropolitan Life Insurance Company tables.

21. This patient was in the hospital for thirteen days before the data recorded on the chart were obtained. His condition was so serious that the intake of fluid had to be restricted. For four days he was on a Karell diet. During this period thoracentesis was performed, and 1,000 cc. of fluid was removed from the right pleural cavity. There was a loss of 21 pounds (9.5 Kg.), from 179 pounds (81.5 Kg.) to 158 pounds (71.7). The results recorded in figure 1, therefore, do not represent the maximum change in this patient from the level of the most extreme heart failure.

The results of dietary restriction may be noted as a considerable slowing of the heart rate (from about 60 to 46 per minute), a drop in both the systolic and the diastolic blood pressure (from about 174 millimeters of mercury systolic and 88 diastolic to 154 systolic and 74 diastolic), a slight increase in the velocity of blood flow, a definite increase in the vital capacity (from 3,300 to 4,100 cc.), a decrease in the respiratory rate (from 12 to 9 per minute, with a decrease in the respiratory minute volume, from about 7 to about 5 liters per minute), a drop of 24 per cent in the oxygen consumption (from about 230 to 175 cc. per minute, representing a decrease in the basal metabolic rate from + 5 to —17 per cent), and a decrease in the cardiac output (about 0.5 liter per minute), associated first simply with lowering of the oxygen consumption and later also with a decrease in the arteriovenous oxygen difference.

The height of the venous pressure is not recorded in the figure, since it was normal even before digitalis was given, having dropped to 53 mm. of water after absolute rest in bed and the administration of morphine. The fluctuation thereafter was between 53 and 72 mm. of water.

No change was observed in the electrocardiograms taken at frequent intervals throughout the period of observation.

There was definite roentgenographic evidence of a decrease in the size of the heart as the result first of digitalis and then of the dietary restriction (fig. 2). This is illustrated in figure 3 in a manner employed by Levy [13] and Stewart and Cohn.[22]

There was no important difference in the response of the heart rate to atropine (0.65 mg. of atropine sulfate injected subcutaneously) before and after the slowing due to the diet.

According to the formula of Evans and Matsuoka,[23] in which the work of the heart is measured largely by the product of the cardiac output and the mean arterial pressure, the work of the heart in this patient was considerably diminished by the diet (from 7.5 to 5.7 kilogrammeters of work per minute), since both the cardiac output and the mean arterial pressure became smaller.

Because patients occasionally complain of weakness following the restriction of food, the strength of the grip was measured in each hand with a dynamometer on many occasions before and during the period of dietary restriction. There was no noticeable change in the muscular strength as measured in this manner.

22. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart, J. Clin. Investigation **11**:917, 1932.

23. Evans, C. L., and Matsuoka, Y.: The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart, J. Physiol. **49**:378, 1915.

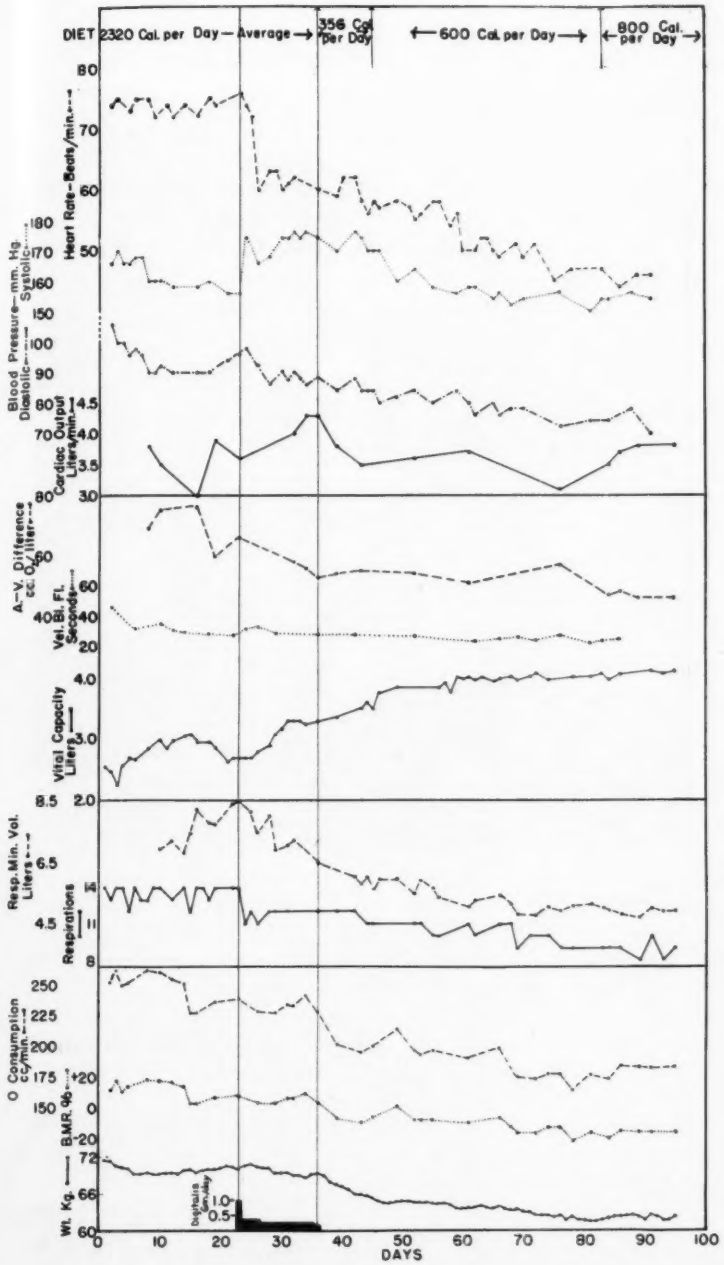

Fig. 1.—Representative results in patient F. C., showing the changes noted before digitalis was given, after digitalis was given and after dietary restriction. Pulsus alternans and Cheyne-Stokes' respiration, both of which were present at the onset, disappeared on the second day after digitalis was given and on the tenth day after dietary restriction was begun, respectively.

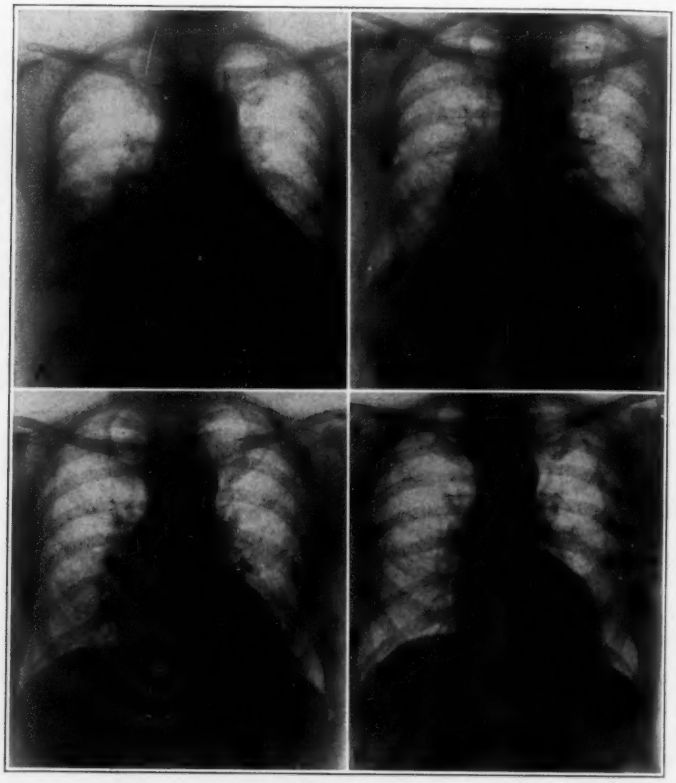

Fig. 2.—Teleoroentgenograms taken of F. C. (*A*) before any treatment was given, (*B*) before digitalis treatment, (*C*) after digitalis treatment and (*D*) after dietary restriction.

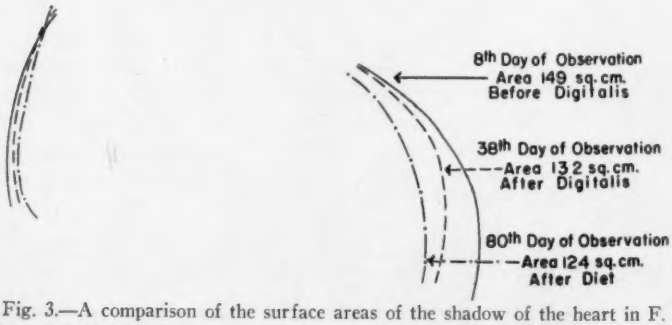

Fig. 3.—A comparison of the surface areas of the shadow of the heart in F. C. before digitalis therapy, after digitalis therapy and after dietary restriction.

In table 2 are grouped the observations on all the patients of the corresponding features, mainly cardiovascular, recorded in figure 1. The changes as given represent those directly attributable to dietary restriction. The values given represent averages over from three to five days. In general it will be seen that in the four men the changes corresponded to those just presented and detailed in the single illustrative case. There was an average loss of weight of 12 per cent, from 147 pounds (66.8 Kg.) to 129 pounds (58.7 Kg.), with a variation from 9.8 per cent to 16.7 per cent. There was evidently no relationship between the extent of the changes and the magnitude of the loss of weight. The average decrease in the heart rate was from 66 to 50 per minute, the variations being from 23 per minute (73 to 50) to 13 per minute (72 to 59).

The average blood pressure, both systolic and diastolic, dropped (from 130 systolic and 71 diastolic to 126 systolic and 60 diastolic). In only one of the patients (M. W.) was there no significant change.

There appeared to be no definite change in the velocity of blood flow, although in one patient (F. C.) there was perhaps a slight increase. The average time required for decholin to reach the taste buds of the tongue from the cubital vein was twenty-seven seconds before and twenty-six seconds after the institution of dietary restriction.

There was a definite and regular increase in the vital capacity, varying from 375 to 750 cc., the average increase being from 3,050 to 3,550 cc.

The respiratory rate diminished almost equally in the four patients, the average being from 15 to 11 per minute. The average respiratory minute volume likewise was considerably smaller after the restriction of food, the average change being from 6.9 to 5.3 liters per minute.

The average fall in oxygen consumption per minute from 237 to 184 cc. represented a more or less uniform change in the four patients. This represented an average drop of 22 per cent. The average decrease in the basal metabolic rate, however, was only 17 per cent (from +8 to —9 per cent). This difference is of course due to the fact that the basal metabolic rate is calculated on the basis of the intake of oxygen per square meter of surface area, and with loss in weight the surface area becomes reduced. If the oxygen consumption diminished in accordance with the diminution in the surface area the basal metabolic rate would in fact be unchanged. Thus the decrease in the basal metabolic rate which takes place when weight is lost represents a greater decrease in oxygen intake than when this occurs with no loss or with a gain in weight. For example, in one case (M. A.), in which a loss of weight of 14 per cent was accompanied with a diminution of the surface area of 10 per cent, there was a decrease in the basal metabolic rate of only 7 per cent, whereas the total oxygen consumption decreased 17 per cent.

In the case of M. W. the initial basal metabolic rate was + 31 per cent. In the absence of congestive heart failure (this was the only patient in whom there were no signs of congestive heart failure when the studies were begun), leukemia, fever and other conditions not due to disorder of the thyroid gland which are known to be associated with elevation of the metabolic rate, a basal metabolic rate of + 31 per cent suggests the presence of hyperthyroidism. However, careful studies revealed no evidence of increased activity of the thyroid gland. We have observed in several patients with enlargement of the heart an apparently unexplained elevation of the metabolic rate. These cases form the subject of another study to be reported on later.

The average arteriovenous oxygen difference was decreased from 60 to 56 cc. per liter. This was associated with a more considerable decrease in oxygen consumption; hence the cardiac output, $\frac{\text{oxygen consumption}}{\text{arteriovenous oxygen difference}}$, also was lessened (from 3.9 to 3.3 liters per minute). The average cardiac output per square meter of surface area (cardiac index) was practically unchanged (from 2.2 to 2.1 liters per minute). The values for the cardiac output and the cardiac index were within the normal range as given by Grollman.[24] There was an increase in the stroke output from 58 to 67 cc.

If the work of the heart is calculated according to the formula of Evans and Matsuoka,[23] it is found that the average decrease in work per minute is from 5.8 to 4.2 kilogrammeters, the decrease in work per beat being from 88 to 80 grammeters.

In three of the men the rest in bed was interrupted a few times each week for the performance for a short period (five minutes) of light exercise on a stationary bicycle. The improvement in the response to exercise after due allowance had been made for the effect of training paralleled the improvement at rest, the decrease following dietary restriction in the pulse rate, respiratory rate and pulmonary ventilation during exercise corresponding proportionately to the decrease at rest noted in table 2. Thus, in the case of M. A. the apex rate during the last minute of exercise, as nearly as it could be counted, was about 200 per minute; after digitalis therapy was added it was 164 per minute, whereas after dietary restriction the apex rate was only 140 during the last minute of exercise. The corresponding change in the respiratory rate was from 27 to 23 to 20 per minute; the change in the pulmonary ventilation was from 45 to 38 to 23 liters per minute; the oxygen consumption during the last minute of exercise (for procedure and technic see footnote 4) decreased from 1,160 cc. per minute before to 1,010 cc. after dietary restriction. The oxygen consumption during exercise was measured only in this one patient. In two of the patients

24. Grollman, Arthur: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

there was a definite improvement in the subjective response to exercise, the patient being able to perform the work with much greater ease. This subjective improvement was not so noticeable in the third patient (M. W.), largely because he complained so much of weakness during the exercise.

In two of the patients the venous pressure had not reached a normal level before the institution of the special diet. In one (C. M.) the venous pressure decreased from 174 to 124 mm. of water after dietary restriction; in the other (M. A.), from 120 to 70 mm.

In table 3 may be seen the relationship in F. C. between the weight, the intake of food, the urinary nitrogen content and the output of urine. The nitrogen in the food was calculated from the protein values as given by Sherman.[25] Analyses of samples of food showed these values to check within 2.2 per cent. The changes chiefly to be noted are the diuresis due to digitalis, though at the time digitalis was given there were no signs of chronic passive congestion, and the negative nitrogen balance as a result of the dietary restriction. Absolute figures for nitrogen balance were not obtained, as the nitrogen in the feces was not measured. Assuming even wide fluctuations in the fecal nitrogen content, a general idea may be gathered of the nitrogen balance from the amount of nitrogen in the food and the urinary nitrogen content. The nitrogen values from table 3 are summarized in table 4, which also contains the values for two other patients, representing two other types of effects of the diet (greater and less loss) on the nitrogen balance. The amount of sodium chloride excreted in the urine also is given in table 4. It is seen that in addition to the loss of nitrogen there was a decrease in the output of sodium chloride, which under the circumstances can be taken to indicate a decrease in the intake of sodium chloride. This decrease in the intake of salt was spontaneous, for there was no restriction, but the decrease was of regular occurrence in all the patients. How important the factors of the loss of nitrogen and the lowered intake of sodium chloride were in the production of the changes noted is impossible for us to determine. It was evident, however, that the magnitude of the changes was not definitely related to the variations in these factors in the different patients. This may be seen clearly in table 4. In the case of M. W. the loss of nitrogen was greater, whereas in F. C. it was small, even during the period of most rigid dietary restriction. Yet the effect on the functional state of the cardiovascular system, as well as on the oxygen metabolism was marked in both cases. On the other hand, in the case of L. McM., who like F. C., showed little loss of nitrogen, the effect of the diet on the circulation was relatively slight.

25. Sherman, H. C.: The Chemistry of Food and Nutrition, ed. 4, New York, The Macmillan Company, 1932.

TABLE 3.—*Daily Observations of the Weight, Intake of Food and Output of Urine in One Patient*

Day of Observation	Weight, Pounds	Intake of Food					Output of Urine, Cc.	Output of Nitrogen, Gm.
		Calories	Protein, Gm.	Nitrogen, Gm.	Fat, Gm.	Carbohydrate, Gm.		
1	158½	2,240	78	11.6	104	253	755	11.9
2	157½	2,603	93	14.8	131	263	740	10.3
3	155½	2,298	93	14.8	106	243	275	4.2
4	155	1,197	54	8.6	65	99	895	11.7
5	154½	1,458	50	8.0	62	175	575	8.5
6	152½	1,949	75	12.0	97	194	580	8.8
7	152½	2,435	103	16.4	119	238	800	10.6
8	153	1,618	68	10.8	82	152	660	9.2
9	152½	1,921	71	11.1	101	182	705	10.2
10	152½	2,501	104	16.6	129	231	715	11.0
11	153	2,081	67	10.7	89	253	665	11.0
12	153	1,662	66	10.5	74	183	870	10.3
13	152½	2,810	102	16.3	146	272	805	10.1
14	154	2,469	99	15.8	153	299	680	7.2
15	154¼	2,483	78	12.4	111	268	665	7.3
16	153	2,506	79	12.6	134	246	450	5.8
17	154	2,898	94	13.4	152	286	1,005	12.7
18	154¼	1,762	66	10.5	74	208	810	9.9
19	154¼	2,507	80	12.8	131	252	565	6.3
20	154½	2,607	93	14.7	123	282	410	4.4
21	155½	2,929	77	12.3	153	311	505	6.3
22	155	1,877	68	10.8	77	183	500	6.5
23	154¼	2,437	85	13.6	113	270	640	7.5
24	156½	2,464	84	13.4	112	280	580	6.6
25	156	1,980	67	10.7	96	212	920	9.3
26	155	1,866	70	11.2	90	194	1,295	10.0
27	154½	2,659	85	13.6	127	294	1,165	9.6
28	154½	2,709	92	14.4	129	295	1,340	6.7
29	153	2,573	76	12.1	113	313	815	7.2
30	155	2,398	80	12.8	114	263	735	7.8
31	153	1,829	71	11.3	85	195	825	8.4
32	152	2,003	77	10.7	103	192	575	7.1
33	152	2,799	87	13.9	127	327	615	8.6
34	151½	2,947	98	15.5	147	308	510	8.5
35	152½	2,583	96	15.3	123	273	705	11.1
36	152¾	2,147	69	11.0	114	211	1,045	12.1
37	152	356	32	5.13	4	48	1,200	9.9
38	151	356	32	5.13	4	48	905	7.2
39	149	356	32	5.13	4	48	630	7.6
40	148	356	32	5.13	4	48	500	7.5
41	147	356	32	5.13	4	48	570	9.2
42	145¾	356	32	5.13	4	48	565	5.3
43	145½	356	32	5.13	4	48	650	6.8
44	145¼	356	32	5.13	4	48	800	6.2
45	144	278	26	4.16	2	39	455	4.6
46	143	601	43	6.88	13	78	385	5.9
47	142½	601	43	6.88	13	78	475	7.6
48	142½	601	43	6.88	13	78	490	6.9
49	142¾	601	43	6.88	13	78	420	5.5
50	143	601	43	6.88	13	78	1,110	10.1
51	143	601	43	6.88	13	78	635	6.2
52	142½	601	43	6.88	13	78	854	7.7
53	142½	601	43	6.88	13	78	815	8.1
54	141½	601	43	6.88	13	78	440	5.3
55	142	601	43	6.88	13	78	680	7.6
56	142	601	43	6.88	13	78	775	7.7
57	142	601	43	6.88	13	78	955	5.9
58	141	601	43	6.88	13	78	795	6.8
59	140½	601	43	6.88	13	78	555	4.9
60	140½	601	43	6.88	13	78	445	4.7
61	140⅛	601	43	6.88	13	78	425	5.9
62	140¾	601	43	6.88	13	78	580	5.0
63	141	601	43	6.88	13	78	425	3.9
64	140½	601	43	6.88	13	78	670	6.7
65	140¼	601	43	6.88	13	78	760	5.1
66	141	609	43	6.88	13	80	695	4.7
67	139⅝	609	43	6.88	13	80	480	4.1
68	139½	609	43	6.88	13	80	830	5.4
69	139¾	609	43	6.88	13	80	...	...
70	139	609	43	6.88	13	80	935	5.7
71	139	609	43	6.88	13	80	660	3.3
72	138	609	43	6.88	13	80	540	4.5
73	137½	609	43	6.88	13	80	750	5.3
74	137½	609	43	6.88	13	80	965	4.8
75	137	609	43	6.88	13	80	1,140	7.2
76	137½	609	43	6.88	13	80	1,135	6.7

TABLE 3.—*Daily Observations of the Weight, Intake of Food and Output of Urine in One Patient—Continued*

Day of Observation	Weight, Pounds	Intake of Food					Output of Urine, Cc.	Output of Nitrogen, Gm.
		Calories	Protein, Gm.	Nitrogen, Gm.	Fat, Gm.	Carbohydrate, Gm.		
77	136½	609	43	6.88	13	80	965	5.4
78	137	609	43	6.88	13	80	985	5.3
79	136¼	609	43	6.88	13	80	915	5.4
80	136	609	43	6.88	13	80	...	...
81	135½	609	43	6.88	13	80	715	6.1
82	136	609	43	6.88	13	80	655	9.0
83	136¾	800	57	9.12	16	107	1,085	6.6
84	137	800	57	9.12	16	107	750	7.4
85	137	800	57	9.12	16	107	870	6.7
86	137	800	57	9.12	16	107	910	5.9
87	137½	800	57	9.12	16	107	1,185	7.1
88	137½	800	57	9.12	16	107	1,010	6.3
89	137	800	57	9.12	16	107	905	5.8
90	136¼	800	57	9.12	16	107	660	6.2
91	137½	800	57	9.12	16	107	920	6.2
92	137	800	57	9.12	16	107	1,150	7.1

Both F. C. and L. McM. had been for at least one week under extreme dietary restriction, because of the seriousness of their condition before our observations were begun. This probably accounts for the positive nitrogen balance before the period of dietary restriction.[8] The unusually great loss of nitrogen in the case of M. W. was unquestionably due to the abnormally elevated basal metabolic rate.

The loss of nitrogen was observed also in the obese patient, being approximately the same as that recorded for L. McM. Of the other two patients, the loss of nitrogen in one (G. W.) was slightly less and in the other slightly greater. It may here be noted that in general the degree to which the various patients complained of hunger corresponded roughly to the quantitative loss of nitrogen.

An excellent opportunity was afforded to study the functional relationship of the cholesterol content of the serum to the basal metabolic rate under the condition of a rapidly changing metabolic rate when this change was not due to the development of myxedema. On the basis of recent reports [26] a lowering of the basal metabolic rate when not due to the production of hypothyroidism might be expected to be followed by no change in the cholesterol content. The actual data may be noted in figure 2. It will be seen that there was a late decrease in the cholesterol content to an abnormally low level associated with a drop in the basal metabolic rate of 22 per cent. The metabolic rate had been at its low level for many days before the cholesterol content changed significantly.

A high level of the protein content of the serum has been reported in the presence of a low metabolic rate in myxedema.[27] This increase

26. Hurxthal, L. M.: Blood Cholesterol and Thyroid Disease: III. Myxedema and Hypercholesteremia, Arch. Int. Med. **53**:762 (May) 1934; Blood Cholesterol and Hypometabolism, ibid. **53**:825 (June) 1934.

27. Decourt, J.; Meyer, L., and Guillaumin, C. O.: Sur le syndrome humoral du myxœdème, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:927, 1935.

TABLE 4.—*Data on the Loss of Weight, Intake and Output of Nitrogen and Output of Sodium Chloride* *

Patient	Sex	Standard Average Weight, Kg.	Period, Days	Average Weight, Kg.	Loss of Weight, Kg.	Food, Calories per Day	Food, Calories per Kg.	Protein Intake per Day, Gm.	Protein Intake per Kg., Gm.	Total Nitrogen Intake, Gm.	Nitrogen Intake per Day, Gm.	Total Nitrogen in Urine, Gm.	Average Nitrogen in Urine per Day, Gm.	Average Sodium Chloride in Urine per Day, Gm.
F. C.	M	71	Preliminary 36	70.3	2.7	2,300	3.3	77.1	1.11	457.1	12.7	324.7	9.0	4.92
			I 9	67.0	4.1	356	5.3	32.0	0.48	45.1	5.0	64.3	7.1	3.83
			II 37	63.5	2.8	605	9.5	43.0	0.68	254.6	6.9	212.0	5.5	3.68
			III 10	62.1	0.0	800	13.0	57.0	0.92	91.2	9.1	65.3	6.5	5.23
L.McM.	F	70	Preliminary 16	55.8	2.6	1,100	20.0	39.0	0.69	98.9	6.2	65.7	4.1	3.59
			I 30	51.9	5.0	356	6.9	32.0	0.60	153.6	5.1	133.4	4.5	2.81
M. W.	M	66	Preliminary 12	65.0	0.8	1,700	25.0	97.0	1.49	130.3	10.9	119.5	9.9	7.18
									0.50	51.2	5.1	91.5	9.2	4.75
			I 10	62.6	3.5	356	5.7	32.0	0.56	49.0	5.4	60.8	6.8	2.40
			II 9	60.3	1.1	598	9.9	34.0	0.79	173.0	7.5	208.2	9.1	3.31
			III 23	59.0	2.0	793	13.6	47.0	0.91	76.3	8.5	77.4	8.6	3.73
			IV 9	58.1	0.0	1,106	19.3	53.0						

* The values for the intake of food during the preliminary period are averages.

was chiefly in the albumin fraction. It is therefore of interest to note (fig. 4) that associated first with the lowering of the basal metabolic rate, yet without any evidence of myxedema, there was an increase in the globulin fraction, the albumin fraction remaining essentially unchanged. Later, however, the albumin fraction decreased, and there was a tendency toward a reversal of the albumin-globulin ratio. There was no albuminuria or evidence of a tendency to retention of fluid. The protein measurements returned to normal when the diet was later increased to 1,200 calories. In figure 4 it will be noted also that the calcium content of the blood, which varied between 9.6 and 10.2 mg.

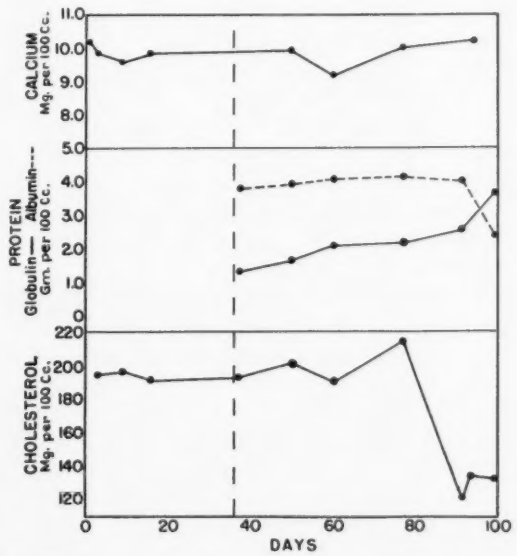

Fig. 4.—Graphs showing the effect of dietary restriction in patient F. C. on the serum cholesterol, blood calcium and serum albumin and globulin contents. The vertical line indicates the beginning of food restriction.

per hundred cubic centimeters on several occasions during the few weeks before dietary restriction was begun, showed no change as a result of the diet, although no calcium medication was given.

The blood sugar content during fasting was decreased (about 15 per cent), although the response to the ingestion of 100 Gm. of dextrose was essentially unchanged.

The hemoglobin and erythrocyte content of the blood, despite the fact that the diet appeared to be deficient in iron, showed no significant changes.

COMMENT

The state of heart failure in a given person is rarely a steady one, and since changes are constantly taking place, owing to many uncontrollable factors, it is extremely difficult to evaluate the effect of a specific procedure, particularly when this procedure involves a period of days or weeks. Since in our studies the patients were at complete rest in bed for many weeks, the question naturally arises as to what the effects of this prolonged rest alone might be. However, since the changes which we have described followed varying preliminary control periods of rest in bed and since these changes regularly began within a few days after dietary restriction was begun, it seems justifiable to attribute these changes to the dietary restriction. It is hoped that this question will be more positively answered from studies which are now in progress on the effects of less strenuous but long continued dietary restriction in ambulatory patients with heart disease.

The effects which we observed to be due to digitalis therapy in the presence of heart failure correspond to those reported by Stewart and Cohn.[22] Attributable to digitalis when given in the presence of heart failure are the following results: an increase in the output of the heart associated with a decrease in the arteriovenous oxygen difference, an increase in the stroke volume of the heart, a decrease in the cardiac rate, a decrease in the size of the heart, an increase in the vital capacity and diuresis. These changes occurred in the presence of both auricular fibrillation and normal sinus rhythm. Since these changes paralleled definite clinical improvement, there can be no doubt that they represented a return of the circulation toward a more efficient state.

Probably the most significant change indicating improvement is the decrease in size of the heart.[28] The procedure further produces benefit by decreasing the necessity of the heart for work. This is made manifest by the decrease in the output of the heart and in the consumption of oxygen as well as by the decrease in the arterial blood pressure. It is entirely possible that the improvement in the function of the heart muscle was the result simply of the decrease in the work of the heart. Yet there are so many other factors involved, such as chemical changes resulting from the reduction of the diet and possibly major fluctuations in the activity of many if not all the glands of internal secretion, that more direct effects on the functioning of the cardiovascular mechanism leading to improvement are not inconceivable.

28. Harrison, T. R.: The Pathogenesis of Congestive Heart Failure, Medicine **14**:255, 1935.

29. Footnote deleted by authors.

One of the more striking effects of dietary restriction that we noted was a slowing of the heart rate. It was this feature which first attracted our attention to the possible value of such a procedure. Harrison, Ashman and Larson [30] have presented convincing evidence of the desirability of producing considerable slowing of the heart rate in the presence of myocardial hypertrophy. On the basis of comparative studies, they stated that they had come to believe that the slow heart rate in animals with thick cardiac fibers is advantageous because the recovery period of the heart is prolonged, i. e., it takes oxygen longer to diffuse through a thick fiber than through a thin fiber. Their evidence also indicated that heart failure may be due in part to a heart rate which is faster than optimal, and they stated in conclusion that their "data suggested further that if it were possible to reduce the cardiac rate to a level considerably below the normal, 'cardiac fatigue' would be much benefited." Wearn [31] likewise, in a demonstration of the relationship between fiber thickness and blood supply, reached the conclusion that, other things being equal, a thick muscle fiber is less adequately supplied with blood and hence oxygen than a thin muscle fiber. Since this supplying of blood is accomplished chiefly during diastole, it is obviously desirable in the presence of hypertrophy for the heart rate to be as slow as possible yet consistent with good cardiac function. The results just presented indicate clearly that a slowing of the heart rate beyond what is possible otherwise may be obtained with prolonged restriction of food.

There is reason to believe on the basis of our observations on patients with heart disease and those of Benedict and his associates on normal persons that in the presence of a normal heart rhythm the slowing of the heart rate which is obtainable by dietary restriction is more regularly observed and is of greater magnitude than that following digitalis therapy.[32] Of our six patients, only three showed a normal rhythm; one of these showed no signs of cardiac weakness (M. W.) and received no digitalis, whereas in another (G. W.) the slowing of the heart rate following digitalis therapy was not striking. That digi-

30. Harrison, T. R.; Ashman, R., and Larson, R. M.: Congestive Heart Failure: XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart, Arch. Int. Med. **49**:151 (Jan.) 1932.

31. Wearn, Joseph T.: The Circulation in Normal and Hypertrophied Hearts, New England J. Med. **212**:1238 (June 27) 1935.

32. (*a*) Robinson, G. C.: The Therapeutic Use of Digitalis, Baltimore, Williams & Wilkins Company, 1923. (*b*) Mackenzie, J.: New Methods of Studying Affections of the Heart: III. Action of Digitalis on the Human Heart, Brit. M. J. **1**:759, 1906. (*c*) Cohn, A. E.: Clinical and Electrocardiographic Studies on the Action of Digitalis, J. A. M. A. **65**:1527 (Oct. 30) 1915. (*d*) Robinson, G. C.: The Value of Large Single Doses of Digitalis in the Treatment of Heart Disease, South. M. J. **13**:396, 1920.

talis may slow the heart rate when the rhythm is normal is shown convincingly in figure 1. In the presence of auricular fibrillation dietary restriction appeared to have an effect in slowing the heart rate comparable to the effect that it has when the rhythm is normal.

It is of some interest to speculate as to the mechanism involved in this slowing of the heart rate. We are inclined to attribute it to diminished sympathetic activities associated with a depression of the functional activity of the adrenal gland. The general state brought about by prolonged dietary restriction appears to be one of universal depression of activity of the endocrine glands, possibly through a diminution in the activity of the anterior lobe of the pituitary gland; hence, such effects as a diminished blood pressure, slower pulse rate, decreased metabolic rate, diminution in sexual desire in men [1] and cessation of the menses in women.[33]

One of the most striking and clearcut evidences of clinical improvement which we observed was in regard to the respiratory exchange and vital capacity. Peabody, Wentworth and Barker [34] and Peabody and Wentworth [35] were the first to point out that an increase of the minute volume of the lungs and a decrease in the vital capacity occurred as heart failure became more pronounced. These studies were later amplified by Harrison, Turley, Jones and Calhoun,[36] who also observed that in patients with congestive heart failure the degree of dyspnea (and hence the extent of weakness of the left ventricle) was proportional to the expression $\frac{\text{ventilation}}{\text{vital capacity}}$, ventilation referring to the respiratory minute volume. Since in our patients the pulmonary ventilation decreased considerably while the vital capacity became significantly greater, the beneficial effect is apparent. The increase in vital capacity alone represents, under the circumstances, positive evidence of an increase in cardiac strength, for the comprehensive researches along this line by Peabody and his associates (1915 to 1922), amply confirmed, have demonstrated that the measure of the vital capacity of the lungs represents perhaps the most important single easily measurable guide of cardiac strength.

33. (*a*) Kurtz, C.: Alimentäre Amenorrhoe, Monatschr. f. Geburtsh. u. Gynäk. **52**:367, 1920. (*b*) Dietrich, H. A.: Kriegsamenorrhoe, Zentralbl. f. Gynäk. **41**:157, 1917.

34. Peabody, F. W.; Wentworth, J. A., and Barker, B. I.: Clinical Studies of the Respiration: V. The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, Arch. Int. Med. **20**:468 (Sept.) 1917.

35. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration: IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

36. Harrison, T. R.; Turley, F. C.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure: X. The Measurement of Ventilation as a Test of Cardiac Function, Arch. Int. Med. **48**:377 (Sept.) 1931.

The most extensive and detailed studies on the effect of prolonged dietary restriction on human beings are those of Benedict and his associates. Their report might have led us to anticipate many of the observations which we made and which we have reported here. In most respects in which similar factors were studied (blood pressure, heart rate, oxygen consumption) our data agreed with theirs, although they dealt with young, healthy persons not confined to bed, whereas our studies concerned older persons with heart disease who were kept in bed. There was surprisingly little variance in the effects observed. Thus, in the six patients whom we studied the decrease in oxygen consumption averaged 18 per cent, whereas in the Y. M. C A. students (squad A) the average decrease in oxygen consumption with a corresponding loss of weight was 19 per cent.[1] Evidently the metabolism tends to respond to influences such as dietary restriction no more in younger persons than in older persons.

One important difference, however, in response in these two groups was in respect to the level of water exchange, as measured by the intake of fluid and the output of urine. We purposely permitted our patients to drink as much water as they desired, in order to observe the spontaneous change which might occur in the level of water exchange. A considerable decrease in the intake of fluid (and hence in the output of urine), such as Benedict and his associates observed in the Y. M. C. A. students, appears to be desirable in patients with heart disease. In only one of our patients, however, was there a diminution in the level of water exchange to a significant degree.

Keeton and Bone,[37] in describing their data on the metabolic effects of the reduction of weight in obese persons, indicated that these effects are not comparable to those observed when the reduction in weight takes place from a normal to an underweight level, i. e., the decrease in the level of oxygen consumption and loss of weight in an obese person is only proportional to and not greater than the percentage decrease in surface area. This is in agreement with the results which we observed in one obese patient (C. M.) whose weight was reduced to a normal level. We may therefore be led to expect a greater physiologic effect on the cardiovascular state, in the presence of heart disease, from a reduction of weight in a patient of normal size than from a reduction of weight in an obese patient. It is self-evident that a fat patient with cardiac weakness should reduce his weight. There may be some hesitancy on the part of the physician, on the other hand, to recommend a reduction in the weight of a patient of normal or low weight. Yet on

37. Keeton, R. W., and Bone, D. D.: Diets Low in Calories Containing Varying Amounts of Protein: Their Effect on Loss of Weight and on the Metabolic Rate in Obese Patients, Arch. Int. Med. **55**:262 (Feb.) 1935.

the basis of our data it appears to be even more desirable that a patient of normal weight with heart disease should reduce his weight.

SUMMARY

Six patients were studied, all save one of whom showed signs of severe congestive heart failure. Observations were made on arterial and venous blood pressure, cardiac rate, velocity of blood flow, cardiac output, respiratory rate, pulmonary ventilation, oxygen consumption, basal metabolic rate, vital capacity, response to exercise, muscle strength, output of urine, intake of fluid, intake and output of nitrogen, output of sodium chloride, red blood cell count, hemoglobin content and blood sugar level. In addition, in the case of one patient repeated measurements were made of the serum protein, cholesterol and calcium contents of the blood. In this case also electrocardiograms and roentgenograms were repeatedly made.

An attempt was made to separate as much as possible the effects of rest in bed and sedatives, digitalis therapy and dietary restriction.

The dietary restriction was such as to effect a loss of weight of approximately 10 per cent over two or three weeks. Restriction was begun with a diet which had a caloric content equivalent to that of the Karell diet. With one exception the weight was reduced from a normal or slightly undernormal level. The one exception was the case in which the weight of an overweight patient was brought to an average level.

The effects attributable to digitalis were slowing of the heart rate, increase in the vital capacity, decrease in the respiratory rate and the respiratory minute volume, increase in the cardiac output with a decrease in the arteriovenous oxygen difference, diuresis and decrease in the size of the heart.

The effects on the cardiovascular and respiratory systems attributable to dietary restriction were further slowing of the heart rate in the presence either of sinus rhythm or of auricular fibrillation, a decrease in the systolic and the diastolic blood pressure even from a normal level, slight or no increase in the velocity of the blood flow, an increase in the vital capacity and a decrease in the respiratory rate and the respiratory minute volume, in the oxygen consumption and the basal metabolic rate, in the cardiac output with slight or no decrease in the arteriovenous oxygen difference, in the venous pressure, in the cardiac work and in the size of the heart. These were changes at rest. There was corresponding evidence of improvement during exercise.

There was a decrease in the level of the blood sugar during fasting, though the tolerance curve was practically unchanged. The hemoglobin content of the blood and the erythrocyte count were unchanged.

In one patient the serum cholesterol content decreased to an abnormally low level after the basal metabolic rate had been at a low level for a few weeks. In this patient also there was first an increase in the globulin fraction of the serum protein with later a decrease in the albumin fraction. There was no change in the calcium content of the blood.

There was evidence of a negative nitrogen balance during the period of extreme dietary restriction (356 calories). There was no relationship between the quantity of nitrogen lost and the magnitude of the changes observed.

There was regularly a decrease in the output of sodium chloride following dietary restriction. In only one patient was the level of fluid exchange (intake of fluid and output of urine) considerably diminished. The intake of fluid and sodium chloride was unrestricted.

In four of the patients considerable clinical improvement was attributed to the dietary restriction; in one the improvement was moderate. This was the patient whose weight was reduced from an overweight level to an average level. In the other patient no significant clinical improvement was observed after the dietary restriction.

Progress in Internal Medicine

GASTRO-ENTEROLOGY IN 1935

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In reviewing the literature on gastro-enterology for 1935 the same policy has been followed as last year. Many original articles have been written on many subjects, but only certain fertile fields have been touched on in this review, and the barren ones have been ignored. Two subjects dealing with peptic ulcer—the treatment of massive hemorrhage and the inadvisability of gastro-enterostomy for uncomplicated duodenal ulcer—have received particular attention. Gastroscopy and gastritis and the recently developed methods of medical treatment for peptic ulcer have not been discussed this year, as it is as yet too soon to draw any mature conclusions about these topics, which were covered in 1934.

ESOPHAGUS

With an improved technic for the roentgen examination of the esophagus and with the wider use of esophagoscopy, more and more clinical attention is being paid to the occurrence of peptic ulcer of the esophagus. Roessler [1] in an excellent review of this subject has tabulated the detailed observations on 72 cases reported in the literature and has added 5 case reports of his own. He has left out the reports of 79 other cases because of insufficient data. In 88 per cent of all the cases of ulcer the lesion was located within the lower 4 cm. of the esophagus, the majority being in the anterior wall. As islands of gastric mucosa are more frequent in the upper part of the esophagus, their presence is not directly responsible for the lesion. A primary disturbance in the function of the vegetative nervous system with a secondary spastic condition and cardiospasm is of greater importance. Vascular spasm with its resulting interference with nutrition is a predisposing factor. Regurgitation of acid stomach contents through the cardiac orifice is of only secondary importance, as it occurs in a variety of conditions without the formation of ulceration.

Esophageal ulcer and its complications may occur without any symptoms at all, just as do peptic lesions elsewhere. As a rule the complaints and the site of pain give sufficient indication of the presence

1. Roessler, W.: Ueber das Ulcus pepticum oesophagi, Deutsche Ztschr. f. Chir. **245**:333, 1935.

of the ulcer to make its localization possible. Pain is the outstanding symptom. It follows eating and even swallowing and is constantly located in the midline, high up in the epigastrium and often under the lower portion of the sternum. Hemorrhage was noted as a symptom in a little over half the cases and was fatal in 14 instances. Functional obstruction and organic obstruction with vomiting are not uncommon, and esophagoscopy with tissue biopsy may be essential to differentiate a peptic lesion from cancer. An ulcer crater may be visualized roentgenographically. Roessler has demonstrated this important diagnostic point with excellent roentgenograms.

The prognosis is not a happy one. The complications of hemorrhage and obstruction often prove fatal. If the ulcer heals, some degree of obstruction follows, owing to the accompanying scarring. Marked improvement in the symptoms occurs, but the patient has them year in and year out. Operative treatment is to be avoided unless obstruction demands it. Esophagogastrostomy has given good results.

Acute ulcerative esophagitis is rarely recognized during life. Bartels,[2] in examining 6,000 autopsy specimens, encountered 82 instances of this condition, an incidence of only 0.013 per cent. He presents a detailed analysis of the pathologic and clinical data and attempts to correlate them. He concludes from the clinical standpoint that esophagitis should be recognized from the symptoms and signs it produces. It commonly occurs in the debilitated but not necessarily dying patient. The inflammation is well localized in the lower third of the esophagus, and it must be accepted that the regurgitation of acid gastric juice into this region is a contributing cause. Vomiting is a common symptom in these cases of acute ulceration and acts as an important factor in permitting the gastric contents to come in contact with the wall of the esophagus. So-called peptic ulcer of the esophagus was not encountered in this entire series of cases.

Since Torek first successfully removed the thoracic portion of the esophagus for carcinoma in 1913 and the patient survived thirteen years, dying of pneumonia, surgeons have hoped to repeat this triumph. Little progress has been made, however, particularly as the operation carries with it a mortality of almost 100 per cent. Consequently, Moersch's [3] description of the successful removal of a carcinoma of the esophagus by surgical diathermy is of special interest. Esophagoscopic examination of his patient revealed a pedunculated tumor the size of a walnut at the junction of the upper and middle thirds of the esophagus, which was destroyed by diathermy. Six months later the patient was perfectly

2. Bartels, E. C.: Acute Ulcerative Esophagitis, Arch. Path. **20**:369 (Sept.) 1935.

3. Moersch, H. J.: Carcinoma of the Esophagus Removed by Surgical Diathermy, Proc. Staff Meet., Mayo Clin. **10**:433, 1935.

well and could eat anything without the least difficulty. He had gained 20 pounds (9 Kg.) in weight. This is apparently the first successful operation of its kind to be reported.

STOMACH

As reports of cascade stomach are meager in the English literature, Upham [4] has reviewed this picturesquely named condition and has outlined the criteria on which a diagnosis may be justified. Cascade stomach, or "shelf stomach," is not to be considered a variety of hour-glass stomach; it is the result of a special change in the form and in the position of the stomach. In both conditions this organ is divided into two parts, but here the similarity ends. In a case of hour-glass stomach, as the term implies, the upper and the lower pocket are of approximately the same size, and one is almost directly above the other. Also the tonicity in these two conditions is the same. In a case of cascade stomach there is dilatation of the upper pocket, which is enlarged posteriorly, and the walls are flaccid. The fluid contents of this large toneless sac in the upper posterior portion of the abdomen splash over into the smaller, more anterior, pocket if the position of the patient is suddenly changed.

Various causes for this phenomenon have been described. In some cases it is anatomic, due to obstruction in the midportion of the stomach, as from a callous ulcer. Great pressure then occurs in the upper sac, displacing the left crus of the diaphragm and other structures which normally occupy the left upper quadrant of the abdomen. In the transitory forms it is spasm of the oblique muscles drawing the stomach up which has been described as the "cup and spill" type. Extreme gaseous pressure or tumor in the splenic flexure of the colon may produce the deformity. It has been said also that it is due to increased gastric pressure from aerophagia. Upham's conception of the cause differs somewhat. The first step is a changed position of the spleen—a lateral displacement, permitting an abnormal mobility of the fornix. This increase in space leads to the second factor; namely, the stomach prolapses posteriorly, rotating on the splenic artery and the tail of the pancreas, causing the damming behind which the cup forms and causing fluid to cascade into the lower pocket. Pressure necrosis of the surrounding fat may exaggerate the abnormal position and increase the obstruction.

Such a conception explains the physical factors by which cascade stomach is acquired, and when pathologic changes are present within the stomach they give rise to a perverted motor function which produces

4. Upham, R.: Cascade Stomach: A Review, Am. J. Digest. Dis. & Nutrition **2**:38, 1935.

the same condition. A typical case is mentioned in which operation was performed. The phrenicogastric ligament was absent, and the spleen was not fixed. The only support of the stomach was at the cardia, allowing it to fall into a lower position than normally and thereby producing the "champagne cup" deformity.

The common symptoms are distention, aerophagy and belching, but the characteristic feature is that the patient is ordinarily completely relieved by lying on the left side, which usually permits the upper pocket to empty. On physical examination there may be prominence of the left side in the region of the eighth, ninth and tenth ribs and in the hypochondrium. The absolute diagnosis depends on the roentgen examination, and the stomach should be examined as a routine with the patient in the left lateral position, as the two pockets may in some measure overlie each other. Medically, there is little of value in the form of treatment, and surgical intervention has rarely brought relief except when intrinsic pathologic changes were present. Antispasmodics may be of value when the deformity is reflex from some other condition.

Seale Harris,[5] of Birmingham, Ala., has written a fascinating report on the gastro-intestinal manifestations of hyperinsulinism. Every physician who reads the present review of gastro-enterology should read Harris' report in the original, as it contains many case histories taken both from the American and from the foreign literature as well as from the author's extensive experience. These are of particular value and of intense interest because the manifestations are so protean in character that they are better appreciated by a careful perusal of a large number of case histories than by any more or less stereotyped textbook form of discussion.

Gastro-enterologists must become "hyperinsulinism conscious," as in most cases the patient connects his symptoms with the stomach. Not only may he have the milder type of gastro-intestinal complaints, but not infrequently he may complain of severe abdominal pains. Several patients have been operated on under a mistaken diagnosis of peptic ulcer, appendicitis or disease of the gallbladder, and hyperinsulinism has been reported coincident with these same disorders as well as with pancreatitis. Although distressing hunger coming on a number of hours after meals and relieved by the taking of food is characteristic, it has frequently led to a false diagnosis of duodenal ulcer. Actually in the cases in which the symptoms are more severe hunger may not be a symptom, and there may be a real disgust for food, amounting sometimes to sitophobia.

5. Harris, S.: Gastro-Intestinal Manifestations of Hyperinsulinism, Tr. Am. Gastro-Enterol. A., 1935, p. 31.

It is again emphasized that while determinations of blood sugar in the fasting state may reveal low values, the results are often normal, and hypoglycemia may be manifest only after a four to six hour dextrose tolerance test. Glycosuria may be found at certain periods, particularly in obese patients, and some may be considered potential diabetic subjects. All low blood sugar values may not be due to hyperinsulinism, as disease of the liver or of certain endocrine glands may lead to hypoglycemia. Studies of the blood sugar content should be carried out in many cases of "nervous indigestion," as a disturbance in sugar metabolism may be an underlying factor in some cases. A carefully planned dietary regimen, usually with a low amount of carbohydrate and high content of fats, often relieves the patient who is suffering from hyperinsulinism.

Gastric Physiology and Secretion.—Oil of peppermint has long held an esteemed position as a household remedy for the treatment of gastric pains and distress. Its use was mentioned during the time of Charlemagne. On account of its popularity Meyer, Scheman and Necheles [6] have studied its action on the secretion and motility of the stomach, utilizing both dogs and human beings. Previous observers have reported that peppermint increases the amplitude and vigor of the contractions of the stomach but has no influence on the secretion of hydrochloric acid. It is stated also that relief from gastric distress is due to an anesthetic action and that oil of peppermint has a cholagogue action. Eating peppermint candy relieves the pain caused by hunger and the distress after a heavy meal.

The authors found that oil of peppermint inhibited the secretion of acid by the resting stomach and greatly reduced its flow after the administration of an alcohol test meal and stimulation with histamine. Most of the 17 patients with peptic ulcer showed depressed or no acidity after the administration of alcohol and oil of peppermint as compared with that after the administration of alcohol alone. Substitution of olive oil failed to produce this change. Study by the balloon method showed that the gastric motility was not depressed by peppermint in physiologic doses. Similar studies by means of roentgenograms revealed a decrease in the emptying time.

As oil of peppermint is a mixture of a number of substances, further tests with its various components will be necessary. The menthol which it contains has no acid depressing effect. A number of patients with peptic ulcer are now under treatment with essence of peppermint, but no conclusions can as yet be drawn, although a few are definitely relieved of pain. If the pain of ulcer is due to local ischemia and

6. Meyer, J.; Scheman, L., and Necheles, H.: Action of Oil of Peppermint on the Secretion and Motility of the Stomach in Man, Arch. Int. Med. **56**:88 (July) 1935.

asphyxia, this essential oil might produce local hyperemia and give relief. This problem is being pursued further.

In considering the rationale of commercial mucin in the treatment of peptic ulcer Baltzer [7] has pointed out that watery mucous soups are superior to mucin preparations as they do not stimulate gastric secretion by their protein content and they do tend to neutralize free acidity. The alleged protective action of ingested mucin does not take place, as the mucin is mixed with the gastric contents. The normal secretion of gastric mucus acts as a barrier between the wall of the stomach and the contents, and medication by mouth cannot duplicate this function.

As achlorhydria is often thought to be a precursor of cancer of the stomach and of anemia, particularly of the Addisonian type, Bloomfield and Polland [8] have made a follow-up report of 45 patients with an unexplained anacidity to histamine. Originally these patients had no gastro-intestinal symptoms of importance, and the absence of free gastric acidity was an incidental finding. From one to seven years later none of them had malignant disease of the stomach or anemia in any form. There was a return of free hydrochloric acid in only 1 of 25 cases.

The late Dr. Eugene Klein, of New York, made extensive studies of gastric secretion. His paper [9] dealing with achlorhydria following partial gastrectomy for ulcer is based partly on clinical observations and partly on experimental observations on dogs. His findings are of particular importance in stressing that the effects of an operation on the stomach should be considered primarily from the point of view of altered function rather than of altered anatomy. Removal of the antrum of the stomach produces achlorhydria in only a certain proportion of cases, because only the secondary or chemical phase of gastric secretion is eliminated and the primary reflex phase through the vagus system, the phase of late intestinal stimulation and the less clearly defined phase of spontaneous secretion apparently dependent on conditioned reflexes remain unaltered. It can readily be shown by studies of the secretion in the transplanted gastric pouch of the dog followed by partial gastrectomy that food fails to produce a secretion of free hydrochloric acid. This achlorhydria is due not to a loss of acid cells, as they are situated in the body and in the fundus of the stomach, but to the loss of the antrum, through which the chemical stimuli of the food (secretogogues) act. However, a small dose of histamine which acts directly on the glandular cells stimulates a normal secretion of

7. Baltzer, F.: Der Magenschleim, Arch. f. Verdauungskr. **58**:33, 1935.

8. Bloomfield, A. L., and Polland, W. S.: The Fate of People with Unexplained Gastric Anacidity, J. Clin. Investigation **14**:321, 1935.

9. Klein, E.: Gastric Secretion: V. Achlorhydria Following Partial Gastrectomy for Ulcer; Studies with Histamine and the Transplanted Gastric Pouch. Arch. Surg. **30**:162 (Jan.) 1935.

hydrochloric acid. In other words, partial gastrectomy does not destroy the ability of the stomach to produce free acid but only interrupts the natural train of events for the secondary phase of the secretion of hydrochloric acid.

Clinically the amount of acid present in the test meal after operation will depend on the following factors: (1) the amount of secretory stimulation which persists which is chiefly vagal and reflex; (2) the relative percentage of secretion which before operation is due to the secondary phase; (3) the amount of neutralizing substances contained in regurgitated duodenal contents, and (4) any changes which may occur in the acid-secreting cells themselves. It is evident then that anacidity will be the result of gastrectomy only when a large proportion of the gastric secretion occurs in the secondary phase, when the primary or vagal phase is not profuse and when a large amount of duodenal regurgitation occurs which can neutralize any small amount of acidity present. When these conditions are reversed acidity will persist. After an operation for duodenal ulcer, acidity is more likely to persist than after an operation for gastric ulcer, because of removal of the first part of the duodenum, which exerts impulses inhibitory to gastric secretion. Section of the left, or anterior, vagus nerve, if added to the operation of gastrectomy, thereby reducing the primary vagal phase, is usually sufficient to produce achlorhydria.

It should be clearly recognized that after gastrectomy the use of histamine as a stimulant to acid secretion instead of a test meal is not comparable to normal physiologic processes. It is a powerful chemical stimulus acting directly on the cells. After its use all but 4 of Klein's 17 patients showed free hydrochloric acid. All these patients showed anacidity to the gruel test meal, which is probably more in line with the conditions under which a patient lives. The use of histamine after partial gastrectomy supplies a stimulus similar to the one which has been removed, and it is really surprising that any subject shows anacidity after its use, as the acid cells are still present. More attention should be focused on the separate phases of gastric secretion in both normal and pathologic conditions.

Occasionally, a case of complicated peptic ulcer is encountered in which surgical treatment is not indicated. One aim of therapy must be to reduce the acid secretion of the stomach to a minimum. Jejunal feeding by stomach tube or even by jejunostomy is recommended, as it is said to lower the acidity of the gastric contents. Appell [10] has tested the validity of this statement by determining the effect of jejunal feeding on gastric acidity and secretion in dogs. He found that any food placed in the jejunum stimulated gastric secretion but that some foods produced greater gastric acidity than others. The degree of

10. Appell, A. A.: Effect of Jejunal Feeding on Gastric Acidity, Arch. Surg. **30**:875 (May) 1935.

acidity was about equal in jejunal and in oral feeding when the dogs were fed three times a day, but when they were fed five times a day acidity was actually higher when food was introduced into the jejunum. From the author's experimental findings it appears that the beneficial results of jejunal feedings reported in certain cases of peptic ulcer were not due to a lowering of the gastric acidity.

A new method of directly observing the development of experimentally produced peptic ulcer in dogs has been described by Harper,[11] of the Mayo Clinic. The ulcers were produced in a loop of intestine forming a fistula from an isolated gastric pouch to the abdominal wall and occurred in each animal operated on. The chemical action of the gastric secretion was found to be of prime importance in initiating and maintaining the lesion; and the increasing vulnerability of the intestinal mucosa the farther it was from the stomach was also demonstrated. An ulcer in an isolated pouch caused loss of appetite, vomiting and loss of weight, just as an ulcer in the main portion of the gastrointestinal tract may cause the same symptoms. Of particular therapeutic interest was the fact that in 5 dogs the development of ulceration was prevented by the introduction into the pouch twice daily of a protective emulsion of gelatin, acacia, olive oil and lecithin and that healing of an already existing ulcer could be accomplished in three weeks by the same procedure.

Rafsky[12] has studied the crystalline elements observed following gastric lavage and their relation to disease of the gallbladder. Photomicrographs of the crystals observed in the gastric contents are compared with crystals observed in the bile and in the stones obtained at the time of surgical exploration. He examined 91 patients—58 per cent came to operation and 22 per cent comprised a normal control group. Crystalline elements were noted preoperatively in appreciable amounts in 87 per cent of the patients operated on and were similar to the crystals in the bile and in the stones removed at operation. These elements were present in less than half the patients in the control group and then only in small amounts. When gastric lavage revealed many cholesterol crystals, together with an abundance of calcium bilirubinate pigment, cholelithiasis was present in 97 per cent of the patients. Three case reports are presented to illustrate the importance of the microscopic examination of lavage washings for crystalline elements in cases in which disease of the gallbladder is suspected.

Peptic Ulcer.—Many articles appear every year on the etiology of peptic ulcer, and most of them add nothing to one's knowledge of this

11. Harper, F. R.: Development and Treatment of Peptic Ulcer: An Experimental Study, Arch. Surg. **30**:394 (March) 1935.

12. Rafsky, H. A.: Stomach Lavage Microscopy as an Aid in the Diagnosis of Biliary Tract Disease, Am. J. Digest. Dis. & Nutrition **2**:214, 1935.

disorder. While Robinson's[13] paper on this subject adds nothing startlingly new, his conception of the relationship of constitutional factors as the underlying cause of this common ailment places this disorder in a somewhat different clinical category from that which is commonly accepted. His analysis is based on observations of 70 patients with peptic ulcer.

His factual information supports the neurogenic theory of "peptic" ulceration. Fear, anxiety and apprehension stimulate the vegetative nervous system to the stomach and duodenum, resulting in hypermotility, hyperchlorhydria and vascular spasm. This spasm leads to thrombosis, ischemia, necrosis and ulceration. Factors such as hyperacidity, focal infection and diet *have absolutely nothing to do* with the etiology of the disease. The racial selectivity of peptic ulcer supports this theory. Peptic ulceration does not occur in lower animals and is rare in the Negro and lesser pigmented races. It is rarely found in members of the Caucasian race under primitive conditions. There is a definite type of so-called ulcer build and personality, which the author describes in convincing detail and which has been generally recognized by the medical profession but only as an impression. The results of physical measurements and character studies show that the "typical ulcer type" of patient is a long, lanky, hyperkinetic person, usually a male, who is probably underweight and who has considerable dynamic energy. Only in a few subjects is it difficult to elicit a history of considerable nervous unrest.

As opposed to ulceration elsewhere in the gastro-intestinal tract, it is emphasized that peptic lesions are localized in a small ulcer-bearing area. In over 95 per cent of the cases of ulcer of the stomach the lesions are bunched together within 2 inches (5 cm.) of the incisura. The few ulcers which occur well outside this area have a different etiology and present a different clinical picture. This limited ulcer-bearing area must be accounted for by some difference in its physiology or structure from that of the surrounding tissues. Anatomically it is this region that has the richest vegetative nerve supply. Pathologic studies reveal that the greatest amount of damage in cases of peptic ulcer is produced beneath the mucosa and that thrombosis is probably responsible for the induration and thickening of the serosa and subserosa. Vascular spasm and thrombosis produce a destructive process which is dry and clean, and this is precisely what is observed in a peptic ulcer. It is clear that the ischemic condition of the submucosal structures cannot be due to hydrochloric acid or pepsin; it is due to a rain of nervous stimuli acting on a small portion of the gastro-intestinal

13. Robinson, S. C.: On the Etiology of Peptic Ulcer: An Analysis of Seventy Ulcer Patients, Am. J. Digest. Dis. & Nutrition **2**:333, 1935.

tract which produces hypertonicity of the vascular bed leading to spasm. Such stimuli are of psychogenic origin and produce hypermotility, hypersecretion and hyperchlorhydria.

Andersen's [14] study of pyloric gastritis in Denmark led him to the belief that this is not a disease entity and that gastroduodenitis not only embraces this condition but is intimately related to the development of peptic ulceration. The pyloric syndrome of recurrent periodic gastric pain relieved by food, hypersecretion, delayed emptying of the stomach, hematemesis, melena and occult blood in the stool is not pathognomonic of chronic ulcer but may be noted in the absence of ulcer when only gastritis is present. Andersen was able to collect reports of 21 cases in which the pyloric syndrome was noted and in which operation was performed and no ulceration was observed. Histologic study of the resected portion of the wall of the stomach revealed pyloric gastritis. These patients had all the classic symptoms of ulcer, and 7 had had manifest bleeding. Andersen then studied 160 patients with peptic ulcer who were hospitalized. They were divided into three subgroups. The first was composed of 88 patients with definite roentgenographic signs of ulcer; the second, of 59 patients without definite signs of ulcer, and the third, of 13 patients who had not been studied roentgenographically. The symptoms in the first two groups were essentially the same. The "pyloric syndrome" occurred more frequently in patients without roentgen signs of ulcer, contrary to the general belief that it is characteristic of peptic ulceration. It was present in 90 per cent of the patients who did not show roentgen signs of ulcer and in only 78 per cent of those who showed positive signs. These findings emphasize the fact that inflammation and not ulceration is the underlying cause of the symptomatology. The late appearance of pain after eating is due to the increased movement of the inflamed gastric wall after the stomach empties.

Recurrent vomiting was a frequent symptom of gastroduodenitis uncomplicated by organic obstruction. Hyperacidity and hypersecretion were as common in the cases of gastroduodenitis without ulceration as in cases of peptic lesions. Six hour gastric retention occurred in the patients who were free from ulceration just as well as in those with ulceration and is in no way helpful as to the differential diagnosis. Six hour retention as a disturbance in motor function also was observed in patients without gastroduodenitis and is not to be used as a criterion of organic disease of the pyloric region. Twelve hour retention is considered of far greater diagnostic significance. As regards bleeding, severe hemorrhage with hematemesis and melena is common in patients with gastroduodenitis without ulceration, but in patients with no history of loss of blood the demonstration of occult blood in the stools is

14. Andersen, T.: Ueber Gastroduodenitis, Acta med. Scandinav. **84**: 185, 1935.

uncommon. In other words, the patient bleeds acutely and profusely as a rule, and there is no chronic oozing of blood. When ulceration or a neoplasm is present oozing is common.

Roentgen examination may definitely determine whether a peptic ulcer is present. However, only the demonstration of the niche is to be accepted as a positive indication of its presence. Indirect evidence and "typical deformity" are not evidence of ulceration and may be encountered in cases of gastroduodenitis alone. Studies of the gastric mucous membrane demonstrated pathologic rugae in all but 4 cases of gastroduodenitis, and similar changes were noted only twice in 77 control cases. The author concludes that the roentgenologist should attempt to diagnose only gastroduodenitis with or without demonstrable ulceration and that the diagnosis of the complicating peptic ulcer should be added only when visualization of the niche is possible.

As peptic ulcer involving the greater curvature of the stomach is uncommon, Matthews [15] has reviewed the literature and has reported on 2 cases of his own. Although reports of 139 cases of ulcer of the greater curvature were found, only 22 cases were described carefully enough to make certain the demonstration of the lesion. Preoperatively in both the author's cases the condition had been thought to be malignant.

It has frequently been stated that peptic ulcer is uncommon in the presence of diabetes mellitus. If this is so, it will be of particular interest because diabetic subjects are notoriously liable to many complications and because vascular changes with thrombosis, which many think the underlying cause of peptic ulcer, are unusually common in diabetes. A. J. Leser [16] has attacked this problem from a statistical point of view. He analyzed the incidence of diabetic patients and of patients with ulcer in a large Viennese clinic over a ten year period. Only 2 of the 119 diabetic patients treated with insulin had peptic ulcer. Both patients were males. Leser found the incidence of peptic ulcer in over a thousand nondiabetic males to be 5.22 per cent, and in 283 females, 1.87 per cent. Autopsy revealed in almost 1,000 nondiabetic subjects that ulcer was present in 20.5 per cent of the males and in 18.5 per cent of the females. In the group of 34 diabetic subjects who came to autopsy, no ulcer was found in a male and only 1 in a female, making an incidence of 0 per cent in males and 4.17 per cent in females. It is apparent then on both clinical and pathologic grounds that peptic ulcer is relatively rare in diabetic subjects but that there is at present no satisfactory explanation of this fact.

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15. Matthews, W. B.: Peptic Ulcers Involving the Greater Curvature of the Stomach, Ann. Surg. **101**:844, 1935.

16. Leser, A. J.: Ueber das peptische Magen-und Zwölffingerdarmgeschwür und Diabetes, Arch. f. klin. Chir. **182**:143, 1935.

The management of severe hemorrhage complicating peptic ulcer of the stomach and duodenum has received a great deal of attention recently. Some of the authoritative articles dealing with such important points as diet, starvation, nutritive intravenous injections, transfusions and surgical treatment differ so widely and positively in their statements of what should and should not be done that they are well worth reviewing as a group. One can conclude only that no standardized form of treatment is the only one that can be successful in all cases and that in certain serious conditions thoughtful consideration of the individual problem presented is necessary before an attempt is made to outline the therapy required.

Tage Christiansen [17] studied 289 cases of massive hemorrhage due to peptic ulcer which were reported during the ten years prior to 1934 in the city hospital of Copenhagen. In presenting a review of the literature on this subject he noted that the mortality in most countries is slightly greater than 10 per cent but that in Scandinavia it is slightly less. The mortality in his series was only 7.9 per cent, with a higher percentage for women than for men. The outlook was far better among patients in whom hemorrhage was the first and only symptom of peptic ulcer, and there was practically no difference in the mortality in cases of short duration and in those of long standing. In the last five years the mortality was almost twice that of the previous five years, despite the much wider use of blood transfusion in treating these patients. Eight of 13 patients who had recently been given transfusions died, and the author not only believes that transfusions have not reduced the number of deaths from massive hemorrhage but even suggests that they may have contributed to its increase. The hemoglobin determination was an important factor in the prognosis. When it was below 60 per cent the death rate was almost four times that when it was above 60 per cent.

Autopsy was performed in 16 of the 23 fatal cases. As 1 (12 cases) or more ulcers were found in each case, diffuse bleeding of the gastric mucosa (gastrostaxis) as a cause of fatal hemorrhage did not occur in this group of patients.

De la Viesca [18] has analyzed 177 cases of copious hemorrhage from the stomach noted at the university clinic in Leipzig over the five year period from 1929 to 1934. In 130 patients, or 73.5 per cent, the bleeding was due to gastroduodenal ulcer; in 24, or 13.6 per cent, to carcinoma, and in 18, or 10.2 per cent, to gastritis. In the few remaining patients it was due to miscellaneous causes.

17. Christiansen, T.: On Massive Hemorrhage in Peptic Ulcer, Acta med. Scandinav. **84**:374, 1935.

18. de la Viesca, P.: Die grosse Magenblutung, Arch. f. Verdauungskr. **58**: 22, 1935.

Heavy bleeding was more common from ulcer of the stomach (19.5 per cent) than from ulcer of the duodenum (7.2 per cent). Observations of the degree of anemia and of the blood pressure were the best guide as to the course of the hemorrhage. The greater number of the patients showed fever, which usually subsided quickly. Ninety per cent of the patients with ulcer had hyperacidity. Repeated hemorrhages occurred in 8.4 per cent, and 27.2 per cent of these patients died. Tests of the stools for occult blood indicated that the bleeding lasted as a rule for from two to three weeks. In 6.6 per cent of these cases of bleeding ulcer death occurred. Over twice as many males as females succumbed. The patients over 40 years old were more liable to death than the younger patients (a ratio of 8:1). As mortality statistics show that the incidence of death from bleeding ulcer is variable, surgical treatment with its high mortality is rarely indicated. It should be considered in cases of a long standing, indurated ulcer which predisposes to erosion of an artery.

Smithies [19] has presented in some detail what he believes to be the necessary treatment for massive gastroduodenal hemorrhage. The immediate therapy is morphine, and no drug is so valuable in physiologic doses. Large injections, i. e., up to from ½ to 1 grain (0.03 to 0.06 Gm.) every two or three hours for several doses, are often required. A patient in shock should receive intravenously one-third or one-fourth the usual amount of morphine given subcutaneously, in order to avoid a delay in absorption. The foot of the bed should be raised. The blood pressure and blood count should be determined immediately.

If vomiting is copious and if large blood clots are expelled, thorough lavage with physiologic solution of sodium chloride at a temperature of 110 F. is indicated in order to put the stomach at rest. The heat of the lavage solution acts as an admirable hemostatic agent. Local applications of ice to the abdomen are detrimental, but hot moist applications over a bleeding focus are favorable. *Feeding by mouth in all its aspects should be strictly interdicted.* The ingestion of food stimulates peristalsis and tends to interfere with the formation of a permanent clot. "Ulcer diets" can be productive of only harmful effects, and the administration of hemostatic agents by mouth also is contraindicated. Nothing by mouth except sips of hot water for at least two days after all evidence of bleeding has disappeared is the rule. The fluid content of the body can be kept up by the known available routes.

For more than twenty years the author has employed a nutrient enema containing salt solution, dextrose syrup and 50 per cent alcohol. Not until two days after the cessation of hemorrhage is food by mouth

19. Smithies, F.: The Treatment of Massive Gastro-Duodenal Hemorrhage, Am. J. Digest. Dis. & Nutrition **1**:803, 1935.

permitted and then primarily carbohydrate and no protein. Little milk is administered, and what is given is citrated or parboiled.

If a patient has had one severe hemorrhage he is potentially a subject for surgical treatment. The stoppage of bleeding by drugs has not been successful, and it may lead to a false sense of security. In the author's experience the most potent agent to stop bleeding from a "spurter" is the intravenous administration of 20 cc. of a 5 per cent solution of calcium chloride or better still prompt transfusion of a large amount of whole blood. If such measures do not control the bleeding within from thirty-six to forty-eight hours, surgical intervention should be urged without further delay, while the danger involved is still moderate. Roentgen examination should not be attempted for at least four weeks after the cessation of hemorrhage.

In an article entitled "Treatment of Haematemesis and Melaena with Food: The Mortality," Meulengracht,[20] of Copenhagen, Denmark, has presented the results he has obtained in 251 cases of peptic ulcer. His reasons for abandoning treatment by starvation and "very cautious feeding" and adopting the "something to eat" regimen were as follows: (1) an exhausted patient may die after a hemorrhage, (2) protracted hemorrhage sometimes stops when the patient is given food and (3) an ambulant patient often recovers from severe melena without changing his diet. Also it seems of questionable value to starve the patient and allow acid gastric juice to collect in an empty stomach. The diet, which is started on the first day of hospitalization, is described in detail. It consists largely of tea, bread, cereals, cheese, eggs, meats, soft vegetables and fruits and rice and tapioca puddings. The patient is fed five times between 6 a. m. and 6 p. m. and is allowed to eat as much as he wishes. Alkalis with hyoscyamus and iron are given three times a day.

Transfusion was necessary in only 12 cases. There were only 3 deaths in this entire series, and 1 of the patients died before the diet could be started. If this case is not included, the mortality was only about 1 per cent. This rate is far lower than that in any other comparable series of cases in any country, as the mortality usually ranges from about 8 to 20 per cent with the ordinary forms of treatment. Hemorrhage is apparently not aggravated by putting an abundance of food in the stomach, possibly because in most cases the bleeding has already stopped with the giving of this diet. Blood appears less persistently in the stools. The patient is well fortified with nourishment by the eighth day after the onset of bleeding, a time when many die, presumably from exhaustion. Recovery from the state of shock is more rapid, and the regeneration of blood proceeds more quickly. Dyspeptic symptoms clear up early, and the patient's stay in the hospital is materially shortened.

20. Meulengracht, E.: Treatment of Haematemesis and Melaena with Food: The Mortality, Lancet **2**: 1220, 1935.

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Transfusion was necessary in only 12 cases. There were only 3 deaths in this entire series, and 1 of the patients died before the diet could be started. If this case is not included, the mortality was only about 1 per cent. This rate is far lower than that in any other comparable series of cases in any country, as the mortality usually ranges from about 8 to 20 per cent with the ordinary forms of treatment. Hemorrhage is apparently not aggravated by putting an abundance of food in the stomach, possibly because in most cases the bleeding has already stopped with the giving of this diet. Blood appears less persistently in the stools. The patient is well fortified with nourishment by the eighth day after the onset of bleeding, a time when many die, presumably from exhaustion. Recovery from the state of shock is more rapid, and the regeneration of blood proceeds more quickly. Dyspeptic symptoms clear up early, and the patient's stay in the hospital is materially shortened.

20. Meulengracht, E.: Treatment of Haematemesis and Melaena with Food: The Mortality, Lancet **2**: 1220, 1935.

MacGuire [21] has presented a concise review of the present day methods of treating bleeding gastric and duodenal ulcer. Emphasis is laid on the value of massive transfusions of 1,000 cc. of whole blood. If this addition to the medical treatment is not successful, operative intervention is indicated. From the standpoint of the surgeon the most important step in dealing with persistent bleeding is to confine his efforts to arrest of the hemorrhage, since a second stage operation eliminates the cause. The possibility of complicating alkalosis with a low chloride and a high urea content of the blood or of vitamin C deficiency with "preclinical scurvy" should not be forgotten.

Hendon [22] advocates the use of continuous venoclysis of dextrose and salt solution for as long as ten days in the treatment of hemorrhage from peptic ulcer. No food is given. He feels that the stomach is put completely at rest by this method of nourishing the patient and that retraction of the clot in the stomach or duodenum is thereby promoted. His results were good in a small series of cases.

Hinton [23] has analyzed 87 cases of massive hemorrhage from peptic ulcer in the hope of giving a more intelligent understanding of the treatment to be employed. It seemed advisable to divide the cases into five groups. In group 1 were 16 patients who bled freely while under competent medical management. Statistics show that with the present trend toward the conservative treatment of peptic ulcer there has been an increase in the incidence of gross hemorrhage. These patients should be operated on when the general condition warrants, as further medical treatment seems futile. In group 2 were 11 patients who first had hemorrhage months or years after a previous operation for acute perforation or chronic ulcer. Under these conditions further treatment should be conservative unless persistent bleeding forces an operation.

Group 3 included the most difficult type of patient to treat, as it consisted of 5 who had been operated on for hemorrhage and who had continued to bleed. One must be guarded in recommending further surgical intervention in such cases. Group 4 included 17 patients in whom severe hemorrhage occurred as the first and presenting symptom. Such an acute hemorrhage is a great menace to life, and over 50 per cent of these patients died despite the usual medical treatment. None of those who recovered had been readmitted to the hospital because of further bleeding. The fifth and largest group consisted of 38 patients

21. MacGuire, D. P.: Bleeding Gastric and Duodenal Ulcers, Am. J. Digest. Dis. & Nutrition **2**:431, 1935.

22. Hendon, G. A.: Treatment of Hemorrhage Caused by Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **2**: 255, 1935.

23. Hinton, J. W.: Massive Hemorrhage in Peptic Ulcer, Ann. Surg. **101**: 856, 1935.

who were admitted to the hospital with hemorrhage and who had a long history of symptoms of ulcer without regulated treatment. Here conservative management is by far the best method of therapy.

Westermann [24] has discussed the surgical aspects of gastroduodenal ulcer complicated by hemorrhage in 50 patients who had been treated over a recent ten year period. The incidence of heavy bleeding was 12 per cent. Massive and recurrent hemorrhages occurred in three fourths of the patients, and to all of these transfusion was given at least once and usually more often. Transfusion was completely ineffectual as a means of stopping hemorrhage, as 10 patients in this series died while in the hospital under rigid medical treatment, in many cases receiving daily transfusions. This has led to the author's opinion that immediate surgical intervention of the direct type is justifiable in a large percentage of cases and will prove permanently successful, preoperative and postoperative transfusion being an essential requirement.

Twenty-six patients are well, 7 have had one or more recurrences and 8 have died. In 26 cases a total of 42 operations were performed in an attempt to stop the bleeding. Posterior gastro-enterostomy was the operation elected in 17 cases. In several of these cases an ulcer or a scar was identified on the anterior surface of the duodenum at the time of operation, and every one of the patients suffered a recurrence of bleeding. Recurrent hemorrhage developed after twenty-four of the operative procedures employed, and death occurred as a direct result of operation or hemorrhage following surgical treatment in 32.5 per cent of the cases. Resection of the ulcer-bearing area seems to be the operation of choice, but this may be preceded by jejunostomy for arrest of the hemorrhage. There are some interesting discussions of this paper which serve as a nice balance for it and should be read.

In reviewing the cause of death in cases of massive hemorrhage from peptic ulcer, Christiansen [25] has noted that sudden death is rare, and, barring other causes of death such as pneumonia or peritonitis, the patient usually succumbs two weeks after the onset of bleeding. In 12 cases autopsy revealed erosion of a fairly large artery, and the time of death varied between three and thirty days. In the majority of cases there was no evidence of active bleeding. In such cases hemorrhage itself could not have been the cause of death in the more strict sense of the term. The true cause of these "late" deaths is obscure, and in Denmark it has been ascribed to "heart exhaustion." The author suggests that some of these patients die of uremia of extrarenal origin and presents 2 case reports to substantiate this assumption. Both of his

24. Westermann, J. J.: Surgical Aspects of Bleeding Gastric and Duodenal Ulcer, Ann. Surg. **101**:1377, 1935.

25. Christiansen, T.: Uremia as Cause of Death in Massive Hemorrhage from Peptic Ulcer, Acta med. Scandinav. **85**:333, 1935.

patients showed marked retention of urea and achloruria following gastric hemorrhage without initial vomiting and without evidence of renal disease. The intake of fluid was adequate. Clinical improvement and a fall in the blood urea content occurred after the administration of a solution of sodium chloride. One patient died on the fifteenth day, but autopsy revealed no evidence of gastro-intestinal bleeding. Death was considered to be due to "gastric uremia." Such a diagnosis is clearly evident in patients with persistent vomiting and loss of chlorides, but these 2 patients did not fall into that category. The exact cause of the achloruria and retention of urea in the blood of the patient who has had copious hemorrhages from a peptic ulcer remains unknown, but evidently uremia occurs and may prove fatal.

Konjetzny [26] has given considerable details in describing his experience not only with the surgical treatment of gastroduodenal ulcer but particularly in treating patients who have been operated on unsuccessfully for this disorder. He has laid special emphasis on the postoperative care of the patient with jejunal ulcer. Primary gastroduodenal resection was performed 106 times and 31 operations were performed in cases in which gastro-enterostomy had previously been carried out.

Two patients were admitted to the Coney Island Hospital, Brooklyn, with the diagnosis of obstructive anuria. Neither complained of any gastro-intestinal symptoms, and both had pain in the lower portion of the abdomen. Both were thought to have retention of urine with rupture of the bladder and were operated on. The first patient proved to have a perforating cancer of the stomach, and the second had a perforating ulcer. Segal and Read [27] in reporting these cases emphasize that complete anuria was the presenting and sole complaint in these cases of perforating gastric lesion, and they suggest that it was due to dehydration secondary to the loss of fluids into the peritoneal cavity by way of the gastric opening.

Another adjuvant to the treatment of a benign peptic lesion has now been added to the lengthy list previously recorded. Rivers [28] has prepared a duodenal extract from the mucosa of the hog and has administered it to 8 patients suffering from gastric or duodenal ulcer. The rationale of this form of therapy is based on three different physiologic principles. First, the duodenal mucous membrane possesses a protecting

26. Konjetzny, G. E.: Erfahrungen bei der chirurgischen Behandlung des Magen-Duodenumgeschwürs und operativer Misserfolge bei diesem, besonders des Ulcus postoperativum jejuni, Arch. f. klin. Chir. **182**:685, 1935.

27. Segal, A. D., and Read, J. S.: Complete Anuria in Perforated Gastric Lesions, Am. J. Surg. **30**:276, 1935.

28. Rivers, A. B.: The Use of Duodenal Extract as an Adjuvant in the Treatment of Benign Peptic Lesions: Report of Eight Cases, Am. J. Digest. Dis. & Nutrition **2**:189, 1935.

mechanism against acid gastric secretions. Second, it contains a substance which stimulates the flow of alkaline bile, and pancreatic juice, which neutralize acid chyme. Third, the recent work of a number of investigators suggests that intestinal mucosa contains a substance which is absorbed and causes inhibition of gastric secretions. As Rivers used this duodenal extract only as an adjunct to the usual forms of treatment, it is impossible properly to evaluate its efficacy, even though his patients did unusually well. From a physiologic point of view this therapy deserves further trial with a larger group of patients under more carefully controlled conditions.

Sequelae of peptic ulcer following both medical and surgical treatment are all too frequent, and their exact nature all too often goes unrecognized. Hinton [29] has called attention to these facts and has reported on 7 interesting cases illustrating them. Particular attention is paid to the incidence of pancreatitis and the difficulties encountered in making an early diagnosis of such an associated disease. The laboratory lends no aid. In the advanced stages a history of changing symptomatology is most important. Pain is more intense and more constant and radiates through the back to both lumbar regions, where tenderness may be elicited. Cases of chronic gastrojejunal ulceration and gastrojejunal colic fistulas also are illustrated. Such sequelae require prompt surgical attention. The author's conclusions should be memorized by every physician. He states: "There is no condition in medicine at present in which clinical judgment plays such an important part in the selection of the method of treatment for the patient as it does in peptic ulcer. Whether the treatment should be medical or surgical is a decision that is based to a great extent on clinical experience."

Pack and McNeer [30] have reviewed the literature on sarcoma of the stomach and add 9 new cases of their own to the 335 recorded up to 1931. Lymphosarcoma is the commonest form and makes up about 40 per cent of the cases. Spindle cell sarcoma and myosarcoma are relatively frequent. The average age of onset is at 46 years, eight years earlier than in carcinoma of the stomach. Also in contradistinction to carcinoma, sarcoma of the stomach is radiosensitive, and roentgen therapy has given some excellent results. Three of the authors' 9 patients are living six, seven and ten years, respectively, after diagnosis of the condition, 2 having had gastric resection and 1 having had roentgen treatment alone.

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29. Hinton, J. W.: Sequelae of Peptic Ulcer Following Medical and Surgical Treatment, Arch. Surg. **31**:137 (July) 1935.

30. Pack, G. T., and McNeer, G.: Sarcoma of the Stomach: A Report of Nine Cases, Ann. Surg. **101**:1206, 1935.

Thompson and Howells [31] report 4 new cases of lymphogranuloma of the stomach and list 11 others from the literature in which treatment by partial gastrectomy was successful. One of the authors' patients was alive and well fourteen years later.

Hodgkin's disease of the stomach is rare. As primary isolated lymphogranulomatosis of this organ it is extraordinarily uncommon, only 7 cases having been recorded in the literature up to 1935. Comando [32] has now recorded in excellent detail an eighth case. His patient was a man 27 years old who had suffered from epigastric pains for three years before he was first seen, on April 26, 1930. The lymph glands and spleen were not palpable. The blood count was normal. Roentgenograms of the stomach showed an infiltrating lesion of the pars media and the pyloric region. Partial gastrectomy was performed. Histologic examination of the tissue removed proved the diagnosis to be Hodgkin's lymphogranuloma. The patient has been perfectly well since then. This report emphasizes that Hodgkin's disease of the stomach may be amenable to operative treatment.

Jones and Carmody [33] have reported a case of lymphosarcoma of the stomach in a child 9 years of age who was operated on and who reported nineteen years later that he was in excellent health. The authors state that survival in this case had been longer than in any case on record and that sarcoma of the stomach has been reported in only 3 other children in this age group. A review of the literature shows that, although lymphosarcoma of the stomach is considered highly malignant, there are a number of cases on record in which the patient lived for more than five years, which is a better outcome than for patients with other forms of sarcoma.

The blood picture characteristic of pernicious anemia has already been recognized as occasionally being noted in association with carcinoma of the stomach. It may be associated with or may be due to benign or malignant polyps arising from the gastric mucosa. Priestley and Heck [34] have reported 3 illustrative cases of bleeding malignant polyps of the cardia which appeared to be instances of pernicious anemia. The tongue was smooth, and the neurologic findings were typical of subacute combined sclerosis of the spinal cord. In the first case there was a single large polyp of the cardia which proved at opera-

31. Thompson, T., and Howells, L. H.: Primary Lymphogranuloma of the Stomach: A Report of Four New Cases, Quart. J. Med. **28**:81, 1935.

32. Comando, H. N.: Primary Isolated Lymphogranulomatosis of the Stomach: Report of a Case, Arch. Surg. **30**:228 (Feb.) 1935.

33. Jones, T. E., and Carmody, M. G.: Lymphosarcoma of the Stomach: Report of a Case with a Nineteen-Year Surgical Cure, Ann. Surg. **101**:1136, 1935.

34. Priestley, J. T., and Heck, F. J.: Bleeding Malignant Polypoid Lesions in the Cardia of the Stomach, Ann. Surg. **101**:839, 1935.

tion to be carcinomatous. The severe anemia responded well to injections of liver extract, and the patient's condition was much improved. In the second case operation revealed multiple gastric polyps proximal to the incisura. Segmental resection was performed, and the patient's condition was improved. The third patient was at first successfully treated for pernicious anemia. Subsequent gastric analysis revealed a quantity of fresh blood, and further roentgen examination revealed a small polyp. At operation the tumor was removed and found to be a polypoid adenocarcinoma. About fifteen months later the patient was well. It was felt that in these 3 patients pernicious anemia was not due to hemorrhage but was coexistent with the carcinoma.

Results of operation for gastric cancer are always of interest, as medical treatment has little to offer. Consequently a late follow-up of 184 patients with carcinoma of the stomach surgically treated at the Mayo Clinic from 1918 to 1931 gives a good insight into the desirability of abdominal exploration. An unusually extensive resection (subtotal gastrectomy) was performed in each case. In 40 cases in which a preoperative roentgenographic diagnosis of a doubtfully operable lesion was made, the lesion was resectable. Thiessen [35] reports that 33 of these 184 patients, or 18 per cent, were living and well five or more years after the operation. It is of further interest that in half of these patients there was involvement of the lymph nodes at the time of the resection.

DUODENUM

Meulengracht has already shown in a series of papers that the antianemic factor in pig stomach which is effective in pernicious anemia is presumably confined to the pyloric glands and is not in the peptic glands of the region of the fundus. It is present also, although in smaller quantities, in the cardiac glands. In a fifth communication on preparations from the duodenum this author [36] has demonstrated that the same antianemic substance is present in dried preparations of pig duodenum and that it possesses a powerful antianemic activity. It is evidently associated with the Brunner glands, which are identical with the pyloric glands, and the author suggests that the pyloric-duodenal region which produces this substance should be known as "the pyloric gland organ." Its presence in the duodenum is of great significance as a probable explanation of why pernicious anemia does not develop in all patients with achylia gastrica and in all patients who have been subjected to gastrectomy.

35. Theissen, N. W.: Results of Subtotal Gastrectomy, Proc. Staff Meet., Mayo Clin. **10**:582, 1935.

36. Meulengracht, E.: Continued Investigations on the Presence of the Anti-Anaemic Factor in Preparations of Dried Stomach Substance from the Cardia, the Fundus and Pylorus, and the Duodenum, Acta med. Scandinav. **85**:79, 1935.

In a paper entitled "Incidence and Significance of the Roentgenologic Niche in Duodenal Ulcer," Burch,[37] of the Mayo Foundation, has tried to shed further light on a moot question. The incidence of a niche as reported by different observers has varied tremendously, the figures ranging from 13 to 90 per cent. In the previous fifteen months 1,489 cases of roentgenologically diagnosed duodenal ulcer were studied at the clinic, and a definite niche was noted in only 17.7 per cent. Compression roentgenography had not added to the percentage obtained by routine examination in their hands. As Berg's incidence of 50 per cent was based on cases in which operation was performed, the necropsy observations were analyzed for 140 subjects with 176 ulcers. Healed ulcers only were present in 67 cases. Only 40 of the whole series of patients, or 22.7 per cent, had a crater capable of exhibition roentgenologically as a niche. The significance of the niche is threefold. First, it is pathognomonic of ulcer. Second, it is practically an unequivocal sign that the ulcer is active. Third, if it diminishes or vanishes, that is indicative of progress or cure.

The frequency of duodenal diverticulum has been little appreciated. Grant[38] has reported its incidence, location and relation to age from autopsy studies. His routine procedure was to fill the duodenum with wax in order to obtain a cast of its structure. In this way he was able to demonstrate a number of diverticula extending into the head of the pancreas which would have eluded detection without this special technic. One hundred and thirty-three subjects were examined, and 15 had a diverticulum of the duodenum. In 4 there were multiple diverticula. All the sacs were of the hernia type, only the mucous membrane with its tunica muscularis mucosae being involved. In all but 1 case the sac sprang from the concave pancreatic portion of the second and third parts of the duodenum and was buried in the substance of the pancreas.

Of 51 persons aged 52 years and under, only 2 had a diverticulum, while of 82 persons over 52 years of age, 13 had a diverticulum. It is evident that diverticulum is much more common after the fifth decade of life and is present in about 1 in every 5 or 6 persons. These figures reported by Grant give an appreciably higher incidence of duodenal diverticulum than any previously given. Photographs of the duodenums of 7 patients are reproduced in the article, including a photograph of the largest diverticulum on record.

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37. Burch, H. A.: Incidence and Significance of the Roentgenologic Niche in Duodenal Ulcer, Proc. Staff Meet., Mayo Clin. **10**:471, 1935.

38. Grant, J. C. B.: On the Frequency and Age Incidence of Duodenal Diverticula, Canad. M. A. J. **33**:258, 1935.

In a clinical treatise on this same subject Célice and Parrot-Manson [39] also have noted that diverticulum of the duodenum is frequent late in adult life and that it usually arises from that part of the duodenum adjacent to the head of the pancreas. Symptoms when present are usually associated with peptic ulcer, cholecystitis or pancreatitis.

The cause of obstructive jaundice is often a difficult diagnostic problem, particularly in an older person. In a patient without colic the possibility of a benign lesion is often forgotten, and cancer is considered the responsible agent. Nicholson [40] has called attention to a cause that is often overlooked—that of a diverticulum of the duodenum. His 66 year old patient had suffered from intermittent jaundice for four and one-half months and came to autopsy without operation. Roentgen examination had revealed the diverticulum. Anatomically it arose from the region of the ampulla of Vater and occluded the common bile duct by pressure on it. Similar cases are cited from the literature.

A patient who was apparently suffering from benign tumor of the duodenum is reported on by Roelsen,[41] but the diagnosis is based on repeated roentgen findings alone and not on an anatomic examination. However, the report is of particular value as it contains an outlined summary of 27 cases of benign duodenal tumor, in most cases a polyp, which have been reported in the literature since 1921. The apparent rarity of the lesion and the importance of roentgenograms in the diagnosis are stressed.

SMALL INTESTINE

The management of jejunal ulcer and the conditions leading to its production have been the subject of a paper by Donald C. Balfour,[42] of Rochester, Minn. A striking feature of jejunal ulcer is its remarkable similarity to duodenal ulcer both as to symptomatology and pathologic process and as to the complications of hemorrhage, perforation and obstruction. Intensive medical treatment should always be tried in the early stage of the ulcer before operation is considered. The surgical management of jejunal ulcer differs from that of duodenal ulcer in that operative treatment of jejunal ulcer, disconnection of the anastomosis, will bring about a cure in all cases. The important decision at the time of operation is to make sure a jejunal ulcer is present, and while this is usually easy the ulcer may be located on the posterior wall

39. Célice, J., and Parrot-Manson: Les diverticules duodénaux, Presse méd. **43**:1313, 1935.

40. Nicholson, W. M.: Jaundice Produced by a Diverticulum of the Duodenum, Bull. Johns Hopkins Hosp. **56**:305, 1935.

41. Roelsen, E.: Benign Tumors of the Duodenum, Acta med. Scandinav. **84**: 439, 1935.

42. Balfour, D. C.: Jejunal Ulcer, Am. J. Surg. **28**:439, 1935.

and may be without induration or evidence of perforation; hence it may be overlooked. In cases of hemorrhage, even if a lesion cannot be palpated, it is good practice to eliminate the anastomosis. Plastic procedures on the anastomosis invite recurrence.

However, in practice the problem of the cure of a jejunal ulcer is of minor importance compared with the control of the disease for which the patient was originally operated on. From this standpoint three types of patients should be considered: (1) those with no primary lesion or with a completely healed ulcer, (2) those obviously requiring surgical management of the primary lesion and (3) those who have already undergone gastric resection. In the first group there is obviously no further need for the gastro-enterostomy, and elimination of the anastomosis is all that is indicated. In the second group the most effective method of controlling the disease is by extensive gastric resection, and this is the operation of choice in treating patients with jejunal or duodenal ulcer. A more conservative operation may at times meet the situation satisfactorily. In the third group, in which gastrectomy has already been performed, the jejunal ulcer should be excised, and the jejunum should be disconnected from the stomach. The stomach may then be reanastomosed to the upper portion of the duodenum. Finally, jejunal ulceration depends largely on the circumstances for which an operation on the primary lesion was performed. Gastro-enterostomy for duodenal ulcer in the case of a young patient with high acidity will be followed by a high incidence of jejunal ulcer.

The remarks on treating duodenal ulcer by gastro-enterostomy which accompany this paper by Balfour are well worth quoting. Frank H. Lahey, of Boston, stated: "I would not wish to have a gastro-enterostomy if I could avoid it." J. S. Horsley, of Richmond, Va., said: "A young man with high gastric acidity and a duodenal ulcer who has an enterostomy in addition to his other troubles is in a very unenviable condition." J. M. T. Finney, of Baltimore, stated: "I have felt that it [gastro-enterostomy] was an essentially unsurgical and unscientific operation."

Under the term primary jejunal ulcer Smith[43] records only those cases in which the lesion was primary in the jejunum and did not follow an operative procedure such as a gastro-enterostomy. Only 25 such cases have previously been described; the author presents each in abstract and adds a report of a case of his own in which the ulcer had perforated. Obstruction alone or in addition to perforation was present in several instances. In all but 3 cases the condition was diagnosed either at operation or at autopsy. In these 3 cases the lesion produced constriction, as noted by roentgen examination. Certain symptoms differ

43. Smith, B. C.: Primary Perforated Jejunal Ulcer, Ann. Surg. **101**:1225, 1935.

from those of gastric and of duodenal ulcer. In cases of primary jejunal ulcer the pain is most often in the left upper portion of the abdomen, is nonradiating and appears at no appointed time as regards meals. It is usually made worse by eating, and at no time is it relieved by taking food or soda.

Sjöberg,[44] of Stockholm, reports an unusual case in which there were symptoms of ileus from retention of iron in the cecum. The patient was anemic and had received about 4 Gm. of reduced iron daily for more than two months. Gastro-intestinal symptoms developed, and repeated roentgenograms of the abdomen showed in the cecum a large contrast shadow which was twice the size of a plum. Intestinal evacuations showed iron, and a few stonelike, rather firm lumps also escaped. Subsequent examination showed that only a part of the iron mass had left the cecum, and parts of it could be identified in the colon.

The author was able to produce a contrast shadow in the intestine in another patient by giving large doses of iron, but no symptoms of ileus occurred.

Intussusception of the small intestine in the adult is a relatively uncommon cause of intestinal obstruction and is usually caused by a neoplasm, which is often benign. The literature on this subject is reviewed by Haggard and Floyd.[45] They present an interesting case report of a boy aged 14 years who had three small intestinal resections for intussusception due to adenoma. There was a remarkable family incidence of intestinal obstruction due to a tumor in this case. The boy's father had four operations for obstruction; in three instances the obstruction was due to neoplasm and in the fourth to a malignant polyp of the colon. The boy's only sister had two operations for obstruction due to a benign growth. The familial phenomenon was strikingly illustrated by this family.

Linitis plastica is a rare but long-recognized lesion of the stomach. That it may also involve the intestinal tract is little known. Stevens,[46] of the Mayo foundation, found reports of only 37 such cases in the literature. He found reports of 6 similar cases in the files of the clinic, and he cites 1 in detail in which obstruction of the large bowel led to a fatal termination. One of his patients was alive eleven years after abdominal exploration, but the other 5 all showed microscopic evidence of a malignant growth.

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44. Sjöberg, H.: Symptoms of Ileus from Retention of Iron in Cecum Following the Administration of Large Doses of Iron, Acta med. Scandinav. **85**:128, 1935.

45. Haggard, W. D., and Floyd, W. O.: Repeated Resections for Intussusception Due to Familial Tumors of the Small Intestine, Am. J. Surg. **28**:428, 1935.

46. Stevens, G. A.: Carcinoma of the Linitis Plastica Type Involving the Intestine, Proc. Staff Meet., Mayo Clin. **10**:349, 1935.

Haggard [47] in his study on appendicitis has remarked particularly on the delayed operation in delayed appendicitis. He has reviewed the results of 3,344 operations for this disease in his own clinic at the Vanderbilt University School of Medicine and analyzed the literature with particular reference to the lack of improvement in the mortality since the time of Reginald Fitz, fifty years ago. The persistent high incidence of postoperative deaths falls largely in the cases of spreading peritonitis which often follows gangrenous perforation of the appendix. Such a sequela is usual in a case of obstruction of the appendix and may well be compared with that of obstruction of the intestine with its dire results. Operation in this stage results in about a 25 per cent mortality.

Theoretically, if every patient with appendicitis could be operated on in the first twenty-four hours the terrible death rate would be a thing of the past. A good surgeon may wisely postpone operation during the "fatal third or fourth day" and may wait until the inflammation has localized or a palpable abscess mass is detectable. There is no conservative treatment in the majority of cases, however, once a purgative has been given. When the patient enters the hospital with a palpable mass, appendectomy and drainage give a mortality of 15 per cent, while drainage alone gives only a 4 per cent mortality. Subsequent appendectomy will be required in about half the latter cases and the death rate is then only a little over 1 per cent. The author emphasizes that appendicitis is an emergency during the first few hours and that operation is indicated at once. Much surgical wisdom must be exercised in deciding for or against opening the abdomen in the cases of delayed development of symptoms, because it is at this time that the great number of fatalities occur following operation.

Schmidt and Taylor [48] wished to compare the conservative and operative methods of treating acute appendicitis. Experimentally they produced acute appendicitis (actually typhlitis) in 48 dogs by ligating arteries or crushing or ligating the base of the organ. Twenty-eight animals survived; 13 of these were operated on, while the rest were given conservative treatment. There was a mortality of only 29 per cent in this second group, while the mortality in the group operated on for acute appendicitis was 52 per cent, the cause of death being peritonitis in the majority of cases. The authors conclude that in dogs the conservative treatment of acute appendicitis shows a lower mortality than operative treatment.

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47. Haggard, W. D.: Appendicitis: An Analysis of 3,344 Cases with Remarks on the Delayed Operation in Delayed Appendicitis, Am. J. Surg. **28**:71, 1935.

48. Schmidt, E. R., and Taylor, A. C.: Acute Appendicitis in Dogs, Arch. Surg. **31**:65 (July) 1935.

A case of a rare condition recognized in German literature under the name pneumatosis cystoides intestinalis has been described by Graberger [49] because he felt that the correct diagnosis could have been made by roentgen examination if that condition had been kept in mind. In cases previously reported on the condition was recognized only at operation or at autopsy. The author's case is the first one in which roentgen studies were made which could be called diagnostic. The cause of these air-containing cysts, which also occur in swine, sheep and chickens, is thought to be bacterial, or, what is more likely, to be due to entrapped air which has entered the loose areolar tissue of the abdomen. The cysts are located in the mesentery, in the omentum under the diaphragm and on the peritoneum and are usually multiple and grapelike. Most of the patients have symptoms of ulcer and often of pyloric stenosis as well.

The author's patient was a woman 39 years old with symptoms suggesting peptic ulcer complicated by pyloric obstruction. Roentgenograms confirmed the clinical impression, and operation proved the diagnosis to be correct. The surgeon found also a 50 cm. portion of the lower end of the ileum which showed typical pneumatosis. A review of the roentgenograms revealed an area the size of the hand in the left flank with an unusual alveolar structure, the preoperative significance of which was unknown. The film of this area is compared in the article with a film of the specimen removed, and this comparison seems to justify the author's conclusion that a preoperative diagnosis of pneumatosis cystoides intestinalis could have been made by roentgenologic examination.

LARGE INTESTINE

A. J. Baker has translated into English the thesis entitled "Vaccine Therapy in Ulcerative Colitis" by Sibrand Lups,[50] of Groningen, Holland. Actually the title is too limited in its scope, as the first part of this thesis deals entirely with the clinical and roentgenologic aspects of the disease and will serve for a long time to come as one of the best monographs on this subject which has yet been written. There is a brief historical review, as well as excellent descriptions of the symptoms and signs, the disturbances in the defecation, the findings in the stools, the examination of the rectum and the sigmoid flexure, the blood picture and the medical and surgical treatment. The outstanding feature of this clinical description is the section on roentgenography. Findings in the catarrhal, ulcerative, nodular hyperplastic and healing stages are discussed and illustrated by pictures which must be seen to be appreciated.

49. Graberger, G.: Beitrag zur Kenntnis des Roentgenbildes bei Pneumatosis cystoides intestinorum, Acta radiol. **16**:439, 1935.

50. Lups, S.: Vaccine Therapy in Ulcerative Colitis, Am. J. Digest. Dis. & Nutrition **2**:65 and 139, 1935.

In the second part of this thesis the author has reviewed the bacteriology of idiopathic ulcerative colitis, with particular emphasis on the work of Bargen with his vaccine therapy. Bargen's diplococcus was injected into 15 rabbits. Most of the animals showed a loss of weight and diarrhea, and at autopsy the lumen of the bowel contained bloody mucus. In nearly all the rabbits the diplococcus was present in the blood stream from forty-eight to seventy-two hours after the injection and was present also in the intestinal mucus. Control animals remained normal. The conclusion is that the diplococcus is able to cause inflammation of the cecum and colon. The strain of organism used was apparently a virulent one.

Case histories are presented of 16 patients who were treated with diplococcus vaccine. Eight recovered completely, and 6 others were improved. These results of autovaccination are concisely outlined in tabular form. Special cultural methods were used for growing the diplococci, greatly facilitating their recovery from the infected colon.

There is little information available as to the exact prognosis of nonspecific ulcerative colitis. The fact that the earlier clinicians called it colitis gravis gives a good insight into what the ultimate course may be. Consequently the follow-up studies of 90 cases of this disease by Crohn and Rosenak [51] are particularly timely. The cases were followed for from two to fourteen years, and the records are up to date in 75 cases. Approximately half the patients had been ill for less than a year and the other half for from two to fourteen years. Of the 90 patients, 44.5 per cent are listed as cured, 29.9 per cent as improved, 10.9 per cent as unimproved and 14.8 per cent as dead. Seventy-five per cent of the entire group were cured or improved. The longer the cases were followed the lower the percentage of favorable results. However, the rate fell only to 62 per cent in the group followed for from six to ten years.

Certain general rules of treatment were followed in all cases. A retention enema of a 1:4,000 solution of acriflavine base in physiologic solution of sodium chloride was usually given nightly. Colonic irrigations were avoided. The diet was liberal and included in all classes of vitamines. Deodorized tincture of opium was employed for excessive diarrhea but in minimal amounts. Since 1921 the intravenous injection of polyvalent antidysentery serum has been employed, but it is recognized that any protein shock and febrile reaction could bring about a beneficial change in the chronic course of the disease. Splendid results followed the authors' method of treatment with a specific serum. It is comparable to Bargen's results with a streptococcus vaccine and serum.

51. Crohn, B. B., and Rosenak, B. D.: A Follow-Up of Ulcerative Colitis (Non-Specific), Am. J. Digest. Dis. & Nutrition **2**:343, 1935.

For surgical treatment ileostomy is the operation of choice, but it should be restricted to cases in which the condition is regarded as incurable under any form of medical therapy. The mortality was 33.5 per cent. The conclusion is that *skilful neglect does not succeed in cases of ulcerative colitis.* A strict and aggressive therapeutic program will bring favorable results in a large percentage of cases in which the condition is supposedly incurable.

As the name of the disease implies, the cause of idiopathic ulcerative colitis remains obscure. It has been stated repeatedly that this condition may be related to bacillary dysentery. Winkelstein and Herschberger [52] have explored the possibilities of this relationship from three points of view. One hundred and twenty patients with nonspecific ulcerative colitis were tested for the presence of the dysentery bacillus, for positive agglutinations with this organism and for a bacteriophage active for one or more strains of the dysentery bacillus group. Bacillus dysenteriae was present in 7 of 60 cases. Positive agglutinations were present in high titer in 27 cases (22 per cent of the whole series). Even further suggestive, if indirect, evidence that these patients have or have had bacillary dysentery is to be found in the identification of a bacteriophage active for dysentery organisms in 36 per cent of 41 cases. The therapeutic implications of these findings are clear, but the treatment of ulcerative colitis with polyvalent antidysentery horse serums has not yet been established as superior to other forms of treatment with foreign protein shock. Bacteriophage therapy is now on trial. These studies suggest that bacillary dysentery may play an etiologic rôle in some cases of nonspecific ulcerative colitis.

After surgical treatment of the colon fatal peritonitis is probably more common than after any other type of abdominal operation. Intraperitoneal vaccination has been introduced in an endeavor to lower the mortality. In the earlier methods it was the aim to produce leukocytosis, but no striking protection of the peritoneum was obtained. At present living bacteria or a vaccine of heat-killed colon bacilli and streptococci is injected intraperitoneally. In this type of vaccination a true immune process occurs in which the peritoneum shares locally, and its protection is thought to be due to local hyperleukocytosis. A number of days pass before this takes place. It is to be borne in mind that the use of a vaccine is only prophylactic and not curative and that it is contraindicated in the presence of peritonitis.

Potter and Coller [53] used a heat-killed Bacillus coli vaccine approximately forty-eight hours before operation on the colon in 79 cases.

52. Winkelstein, A., and Herschberger, C.: Studies on the Relation of Non-Specific Ulcerative Colitis to Bacillary Dysentery, Am. J. Digest. Dis. & Nutrition **2**:408, 1935.

53. Potter, E. B., and Coller, F. A.: Intraperitoneal Vaccination in Surgery of the Colon, Ann. Surg. **101**:886, 1935.

Two hundred million bacilli were suspended in 1 per cent tragacanth in physiologic solution of sodium chloride prepared in ampules of 30 cc. each. This preparation diffuses extensively through the peritoneal cavity and is not absorbed too rapidly. In most cases fever and pronounced leukocytosis developed. At operation 73 per cent of the patients showed definite hyperemia of the bowel, omentum and mesentery; an increased amount of peritoneal fluid was present in 31 per cent, and in 24 per cent a true exudate occurred with the appearance of generalized peritonitis. Although 11 patients died, in only 1 instance was death due to peritonitis. Such a low incidence of peritonitis seems to justify the use of the vaccine as a valuable adjunct in the preparation of a patient for an operation on the colon. Its usefulness is in protecting the peritoneum against minor degrees of soiling and infection, but not against gross fecal contamination.

Spontaneous perforation of a diseased ulcerated cecum is well recognized, but it is not generally realized that a diastasic perforation, or "blow out," of an overdistended but otherwise normal cecum may occur as a result of distal obstruction. Few such cases have been described, but Saeltzer and Rhodes [54] have reported 5 instances of this unusual and dramatic accident. Four of these were due to cancer involving the sigmoid flexure, one of which was extrinsic from the ovary and another to cancer of the splenic flexure. They conclude that necrosis and perforation are most often due to some vascular impairment dependent on a preceding infectious process, and the medial wall is the usual site of the break because it is mechanically weaker. In 1 of their cases the obvious tear was apparently due to mechanical violence alone.

In 2 reports, 1 on the colon and 1 on the rectum, Raiford [55] has presented a complete analysis of carcinoma of the large bowel. Five hundred and eleven patients admitted to the Johns Hopkins Hospital in the forty-two year period since 1889 were observed. In 192 cases the lesion was in the colon and in 319 in the rectum. In 72 cases it was located in the descending colon and sigmoid flexure and in almost as many, 67, in the cecum and ascending colon. Five year postoperative "cures" were obtained in 32.2 per cent of the cases of operable carcinoma of the colon and in 23.2 per cent of the cases of rectal carcinoma. As the analysis is presented in detail and reveals a number of important facts, the original papers should be used as an up-to-date reference on this subject.

54. Saeltzer, D. V., and Rhodes, G. K.: Diastasic Perforation of the Normal Cecum Resulting from Obstruction of the Normal Colon, Ann. Surg. **101**:1257, 1935.

55. Raiford, T. S.: Carcinomas of the Large Bowel, Ann. Surg. **101**:863, 1935.

Under the title "Simple Hemorrhagic Proctitis and Proctosigmoiditis" Thaysen [56] has described a condition of the lower bowel which occurs relatively frequently but which has received no recognition until recently. It is not to be confused with an ulcerative condition and is limited to the sigmoid flexure and rectum. The bleeding is usually thought to be due to hemorrhoids, and rectoscopy is imperative for an accurate diagnosis. Direct inspection of the rectal mucous membrane when the inflammatory condition is fully developed shows it to be swollen, deep red and finely granular. It bleeds easily. No ulceration or distinct erosions were noted in the 20 patients examined by the author. Microscopically the mucous membrane is the site of marked cellular infiltration and greatly engorged vessels, but abscess formation and necrosis are absent. The accompanying figures illustrate the lesion nicely. Stenosis and thickening of the rectal wall do not occur even in cases of involvement of long standing.

This form of proctitis is most common in young adults. The one common symptom is free bleeding in small amounts, ordinarily accompanying the stool. As the disease is chronic and recurrent some purulent mucus may appear. Slight constipation is the rule. In cases in which the condition is uncomplicated there are no other symptoms, and fever rarely occurs. Rectal examination reveals only blood and mucus on the examining finger and the absence of hemorrhoids which might be held responsible for the symptoms. Blood may be on the outside of a lumpy stool, or it may follow its passage and be entirely separated from it. Anemia is only moderate, if present, despite the long duration of the disease and the repeated hemorrhages. Gastric analysis and roentgen examination are of no aid in the diagnosis, which must be based on rectoscopy. Confusion with hemorrhoids, polyposis or ulcerative colitis can be cleared up only by direct inspection of the wall of the lower portion of the large bowel. The etiology of simple hemorrhagic proctosigmoiditis is unknown. In Denmark this condition occurs more frequently than ulcerative colitis.

The treatment is partly local and partly general. Local instillations of a 1 per cent solution of chiniofon produces good immediate results which may be striking. Such treatments must be given daily for an average of two months. In some cases this form of therapy may fail, and relapse often occurs later. General treatment consists of rest in bed, sedatives and the combating of constipation. As regards the prognosis, no patient has died; serious relapses are rare in the cases in which treatment is instituted, and the patient who has had a mild relapse responds well to therapy. However, a relapse may occur even after the patient has been free from bleeding for four years.

56. Thaysen, E. H.: Simple Hemorrhagic Proctitis and Proctosigmoiditis. Acta med. Scandinav. **84**:1, 1935.

INTESTINAL PARASITES

Intestinal infestation with Giardia intestinalis is not rare among the inhabitants of the temperate zones. MacPhee and Walker [57] have studied the pathogenicity and symptomatology of the infection caused by this parasite in a series of 732 patients observed in New England. This miscellaneous group of patients presented a variety of gastro-intestinal complaints, and routine examination of the biliary drainage was made in each case. Giardia were present in only 6 cases, an incidence of slightly less than 1 per cent. Perhaps in the majority of cases the infection may occur without causing complaints which might lead to their detection. Five of the authors' cases are presented, but therapy was carried out to eradicate the parasites in only 1 instance. This patient's condition was improved. The authors present some important conclusions based on their own studies and on a review of the literature.

A variety of symptom complexes occur, but in the cases of more severe involvement they are more biliary than intestinal. In almost all instances there are nausea and pain of varying severity in the upper portion of the abdomen; less frequently there are jaundice, enlargement of the liver and tenderness of the gallbladder. There is no accompanying eosinophilia. The gallbladder has been removed in many cases without affording relief from the symptoms. Microscopic examination of fresh duodenal contents readily reveals the parasites. Stool examinations are less successful. Giardiasis should be considered in all cases in which cholecystectomy for chronic cholecystitis or cholesterosis seems indicated but in which there is no definite evidence of gallstones.

Although there are many statements to the contrary, Giardia is clinically pathogenic. Usually the habitat of the organisms is limited to the duodenum and jejunum, but they have been demonstrated in the bile ducts and in the gallbladder. Various forms of antiprotozoa therapy have been successful. The authors used thymol. A reduction in the number of organisms will alleviate the symptoms, but cure by means of their complete eradication is rare.

G. S. de Paula e Silva,[58] of Bello-Horizonte, Brazil, has presented a clinical study of 22 patients with giardiasis seen in private practice. These represent 3.8 per cent of 572 patients seen over a two year period. The incidence of this parasitic infestation is thought to be much higher in clinic patients (i. e., the poor). The diagnosis was based on the presence of Giardia (lamblia) in the bile obtained by duodenal drainage.

57. MacPhee, L., and Walker, B. S.: Intestinal Giardiasis in New England, with Notes on Its Pathogenicity and Symptomatology, Am. J. Digest. Dis. & Nutrition **1**:768, 1935.

58. de Paula e Silva, G. S.: A Clinical Review of Giardiasis: Twenty-Two Cases Observed During Study of Five Hundred and Seventy-Two Private Patients, Am. J. Digest. Dis. & Nutrition **2**:350, 1935.

Cysts of Giardia were present in the stools in only 54 per cent of the cases, when only one specimen was examined. In 1 instance fifteen repeated stool examinations gave negative results.

Certain symptoms were so frequent in these patients and so constantly disappeared after eradication of the parasites that, contrary to the common belief, the author feels that intestinal infestation with Giardia causes definite symptoms. These have been divided into three groups: those attributable to involvement of the biliary tract, with dyspepsia and severe pains like gallstone colic; those suggesting extensive infestation of the intestine, with diarrhea often a feature, and those which are polymorphous and systemic. Two patients had high fever. One presented jaundice, but it was not attributable to giardiasis. The author insists that giardiasis should be treated and outlines his technic in detail. After good drainage of the biliary tract, neoarsphenamine is given intravenously at five day intervals for from twenty to twenty-five days. During this time acetarsone and chiniofon are given by mouth. The results of this therapy are good. The condition appears to be clinically cured. Fourteen of 16 patients were free from parasites seven months after treatment. Failure was apparently due to inadequate treatment. The author recognized the possibility that relapses may still occur.

Although infestation with Ascaris is usually considered benign, Genkin [59] has described the case of a 12 year old girl with volvulus caused by an enormous mass of the worms which blocked the bowel. Operation was successfully performed, and 800 ascarides were removed. The author states that this is larger than any number of these parasites that has been reported in the literature.

Adams,[60] in Mauritius, has reported an unusual case of ascariasis of the liver in which the patient came to autopsy after exploratory laparotomy for an acute abdominal condition. The hepatic duct was observed to be torn open by the passage through it of an ascaris worm. Seven adult worms were found in the gallbladder and four more in the liver, and numerous eggs were present in the parasitized bile passages.

59. Genkin, I. I.: Ein Fall von Ascariden volvulus, hervorgerufen durch eine enorme Menge von Ascariden, Arch. f. klin. Chir. **182**:642, 1935.

60. Adams, A. R. D.: Ascariasis of the Liver, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:419, 1935.

News and Comment

THE AMERICAN BOARD OF INTERNAL MEDICINE, INC.

The American Board of Internal Medicine, which was incorporated on Feb. 28, 1936, completed its organization on June 15. The officers chosen were Dr. Walter L. Bierring, Des Moines, Iowa, chairman; Dr. Jonathan C. Meakins, Montreal, Canada, vice chairman, and Dr. O. H. Perry Pepper, Philadelphia, secretary-treasurer. These officers and the following six members constitute the present membership of the board: Dr. David P. Barr, St. Louis; Dr. Reginald Fitz, Boston; Dr. Ernest E. Irons, Chicago; Dr. William S. Middleton, Madison, Wis.; Dr. John H. Musser, New Orleans, and Dr. G. Gill Richards, Salt Lake City.

The term of office of each member will be three years, and no member may serve more than two consecutive three year terms.

The organization of the board is the result of effective effort on the part of the American College of Physicians in conjunction with the Section on Practice of Medicine of the American Medical Association, and these two organizations are represented in the membership of the board in a five to four ratio.

The American Board of Internal Medicine had previously received the official approval of the two bodies fostering its organization, as well as that of the Advisory Board for Medical Specialties and of the Council on Medical Education and Hospitals of the American Medical Association.

The purpose of the board will be the certification of specialists in the field of internal medicine and the establishment of qualifications with the required examination procedure for such certification.

While the board is at present chiefly concerned with the qualification and procedure for certification in the general field of internal medicine, it is intended to inaugurate immediately after July 1, 1937, similar qualification and procedure for additional certification in certain of the more restricted and specialized branches of internal medicine, such as gastro-enterology, cardiology, metabolic diseases, tuberculosis and allergic diseases. Such special certification will be considered only for candidates who have passed at least the written examination required for certification in general internal medicine. The operation of such a plan will require the active participation and cooperation of recognized representatives from each of such special fields of medicine.

Each applicant for admission to the examination in internal medicine will be required to meet the following standards:

General Qualifications

1. Satisfactory moral and ethical standing in the profession.
2. Membership in the American Medical Association or, by courtesy, membership in such Canadian or other medical societies as are recognized for this purpose by the Council on Medical Education and Hospitals of the American Medical Association. Except as here provided, membership in other societies will not be required.

Professional Standing

1. Graduation from a medical school of the United States or Canada recognized by the Council on Medical Education and Hospitals of the American Medical Association.
2. Completion of an internship of not less than one year in a hospital approved by the same council.
3. In the case of an applicant whose training has been received outside the United States and Canada, presentation of credentials satisfactory to the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association.

Special Training

1. Five years must elapse after the completion of a year's internship in a hospital approved for the training of interns before the candidate is eligible for examination.

2. Three years of this period must be devoted to special training in internal medicine. This requirement should include a period of at least several months of graduate work under proper supervision in anatomy, physiology, biochemistry, pathology, bacteriology or pharmacology, particularly as related to the practice of internal medicine.

   This work may be carried on in any domestic or foreign medical school or laboratory recognized by the Council on Medical Education and Hospitals of the American Medical Association as offering appropriate facilities for this type of postgraduate experience; or it may include a period of at least several months of graduate work under proper supervision in internal medicine or in its restricted and specialized branches in any domestic or foreign hospital, clinic or dispensary recognized by the council as offering appropriate facilities for this type of postgraduate experience.

3. A period of not less than two years of special practice must be spent in the field of internal medicine or in its more restricted and specialized branches. The American Board of Internal Medicine does not propose to establish fixed rules for the preliminary training of candidates for certification in this field. Broad, general principles for training, however, may be outlined, although such suggestions as are made must, of necessity, be subject to constant changes reflecting the dynamic nature of the specialty.

   A sound knowledge of physiology, biochemistry, pharmacology, anatomy, bacteriology and pathology, so far as they apply to disease, is regarded as essential for continued progress of the physician who practices internal medicine. The mere factual knowledge of medicine and its basic sciences is not sufficient. The candidate must have had training in their use in furthering his understanding of clinical medicine. This implies practical experience under the guidance of older men who bring to their clinical problems ripe knowledge and critical judgment. Preparation to meet this requirement adequately may be even more difficult to obtain than the so-called scientific training. It may, however, be acquired in the following ways:

   a. By work in a well organized outpatient clinic of a hospital, conducted by competent physicians.

   b. By a prolonged period of hospital residency, likewise under the direction of skilled physicians.

   c. By a period of training in intimate association with a well trained and critical physician who has taken the trouble to teach and guide his assistant rather than to require him to carry out the minor drudgery of busy practice.

4. The board does not consider it to the best interests of internal medicine in this country that rigid rules be made as to where or how the training as outlined is to be obtained. Medical teaching and knowledge are international. The opportunities of all prospective candidates are not the same. Some may have the opportunity of widening their knowledge by a period of study abroad; others, at the other extreme, may be restricted to a comparatively narrow geographic area, and their detailed training must be obtained in short periods scattered over a long time. Although it is required that at least five years must elapse between the termination of the first year of internship and the time when the candidate is eligible to take the examination, a longer period is advisable. The board wishes to emphasize that the time and training are but means to the end of acquiring broadness and depth of knowledge of internal medicine which the candidate must demonstrate to the board in order to justify it in certifying that he is competent to practice internal medicine

as a specialty. The responsibility of acquiring the knowledge as best he may rests with the candidate, while the responsibility of maintaining the standard of knowledge required for certification devolves on the board.

Method of Examination

The examination required of candidates for certification as specialists in internal medicine will comprise part 1 (written) and part 2 (practical or clinical).

Part 1. The written examination is to be held simultaneously in different sections of the United States and Canada and will include:

a. Questions on applied physiology, physiologic chemistry, pathology, pharmacology and the cultural aspects of medicine, and

b. Questions on general internal medicine.

The first written examination will be held in December 1936, and candidates successful in this written test will be eligible for the first practical or clinical examination, which will be conducted by members of the board near the time for the annual session of the American College of Physicians at St. Louis in April 1937. The second practical examination will be held at Philadelphia near the time of the annual session of the American Medical Association in Atlantic City, N. J., in June 1937.

The fee for examination is $40, which must accompany the application, and an additional fee of $10 is required when the certificate is issued.

Application blanks and further information can be obtained by addressing the office of the chairman, Dr. Walter L. Bierring, 406 Sixth Avenue, Des Moines, Iowa.

Book Reviews

El problema de la infección focal de las amígdalas y su importancia en medicina: Prueba personal para el diagnóstico y técnica más conveniente para la amigdalectomía. By Dr. Rafael Romero Rodríguez. Paper. Price, 7 pesetas. Pp. 165. Seville: Imp. de la "Divina Pastora," 1935.

A page from Dr. Romero Rodríguez' clear, though brief, treatise on the tonsils and tonsillectomy when they are the site of focal infection, in which he notes the "100 per cent tonsillectomized portions of the United States" as "an exaggeration appropriate only to that country," might well be translated for the benefit of American tonsil specialists. His careful and time-consuming tests for the proof of tonsillar infection, local or focal, may seem unusual to the average American physician. In order to make a diagnosis of focal infection of the tonsils he depends on: (1) the bacterial examination of the caseous material expressed from the crypts, and (2) the test of Viggo Schmidt; a leukocyte count, and the temperature before and after a two minute massage of the tonsils with the finger. If the tonsil is healthy, massage produces leukopenia in about twenty minutes; when infection is present, leukocytosis and a rise in temperature are noted. The Romero tonsil cleansing test is less likely than the Viggo Schmidt test to cause trouble; it is reliable as an aid in making a diagnosis of focal infection in the tonsil. The tonsil is emptied (the open crypts) by massage with a fenestrated depressor and syringed with saline solution. Symptoms that are due to tonsillar infection—low fever, cardiac irritability, myalgia and headaches—disappear and then return after a week or more. If another cleansing is followed by the subsidence and recurrence of the symptoms, one is able to guarantee that benefit will be derived from tonsillectomy. Of course no such test is made during the height of the activity of an infection.

The author's technic of tonsillectomy is one of dissection, as the tonsils he advises to be removed are those characterized by fibrosis, with a prolonged upper pole. Burial of the tonsils under the pillars makes the Sluder method useless. One wonders, however, while reading the excellent description of a disturbing hemorrhage, why it would not be best to finish with one of the crushing technics.

Chapters on disorders due to focal infection in the tonsil (arthritic, renal and allergic) give brief reviews of American and other work. It is clearly stated that the tonsil is the best ally of the streptococcus. The tonsil when acutely inflamed hinders bacterial invasion. This usefulness is lost when it becomes a septic focus. Endocarditic, renal and arthritic conditions subside after tonsillectomy, and cure may be effected. However, these metastases may have sufficient vitality to sustain the infection, especially when their treatment is neglected after tonsillectomy. A list of selected case histories is given.

This is a book that internists and specialists will find worth reading.

Medical Treatment of Gallbladder Disease. By Martin E. Rehfuss, M.D., Clinical Professor of Medicine at Jefferson Medical College, and Guy M. Nelson, M.D., Instructor of Medicine at Jefferson Medical College. Pp. 465, with 113 illustrations. Cloth, $5.50 net. Philadelphia: W. B. Saunders Company, 1935.

This work is based on experience with 908 patients with disease of the gallbladder who were treated medically during the past ten years. Rehfuss and Nelson, however, give no analysis of data as to the results of such treatment or as to its individual elements. One hundred and twenty pages are devoted to the diagnosis of cholecystitis, much emphasis being placed on the results of duodenal intubation and cholecystography in diagnosis and in observation of the

course in the patient under treatment. The catalog of symptoms described as suggesting cholecystitis leaves one with the impression that various other conditions, mostly functional, may have been included by the authors under the class of mild cholecystitis, and this perhaps helps explain their enthusiasm for medical treatment.

The authors feel that the present knowledge of the physiology and pathology of the biliary tract justifies outlining a system of treatment which would be on a rational basis. The pathogenesis is considered extensively from the standpoint of a metabolic disorder, infection and stasis in the biliary tract. The authors outline their plan of therapy for these disturbances, which emphasizes diet (low in cholesterol and fat), repeated duodenal drainage, the eradication of focal infection, the administration of vaccines, bacterial filtrates, cholagogs and choleretics and the correction of constipation. A diet low in fat is usually advised, but if there is evidence of stasis in the biliary tract (determined by the results of duodenal intubation and cholecystography) fats are given to stimulate the function of the gallbladder. A chapter on jaundice by Cantarow outlines this complication adequately. A chapter is also devoted to the medical management of the patient with cholelithiasis.

It is difficult to understand the authors' enthusiasm for medical treatment, especially for drugs and vaccines and similar forms of therapy. Many will find it difficult to appreciate that a 465 page monograph could be developed pertaining to the medical treatment of cholecystitis and cholelithiasis. In general, the reviewer feels that he would hesitate to recommend this book.

Manuel de coprologie clinique. By R. Goiffon. Third edition. Price, 28 francs. Pp. 274, with 42 figures and 3 plates. Paris: Masson & Cie, 1935.

Goiffon's manual on the clinical study of the stools is divided into four parts. Part 1 is devoted to a brief introductory discussion of the normal physiology and digestion concerned in alimentation. This discussion, though inadequate from the physiologist's point of view, satisfactorily serves its purpose in a manual.

Part 2 includes a good presentation of the various forms of quantitative and qualitative analyses of the stool. The proper collection of a specimen and many other points that were formerly considered insignificant are described. More than one technic of analysis as well as the author's technic of preference is presented with the study of each factor. He thoroughly covers the subject of analysis of the stool, beginning with a discussion of its physical characteristics and including such subjects as macroscopic and microscopic material, chemical studies for its reaction, albuminous substances, blood, porphyrine, bile, phenols, indole, fats, ferments (such as catalase, trypsin, amylase and other digestive ferments), animal parasites, bacteria and many more factors which may be of interest to the clinician. Goiffon correlates the findings with normal and disturbed gastro-intestinal physiology and interprets them in terms of health and disease.

Part 3 is devoted to various disturbances in the gastro-intestinal function and to the changes in the stools that may be expected to be revealed on careful examination. Among the conditions discussed are gastric, biliary and pancreatic insufficiency, the colitides and motor dysfunction. He groups with each clinical syndrome the findings in the stool which are most often noted. He emphasizes the fact that the results of an examination of the stool are only an adjunct to the clinical picture, yet an important one.

Part 4 includes a brief review of the treatment of various gastro-intestinal disturbances which are responsible for changes in the stool. Goiffon makes no attempt to cover the entire subject of treatment in gastro-intestinal disease but does attempt to show how proper treatment is usually reflected in the stool by changes toward the normal.

The manual is well written, is very inclusive and is easily comprehended. Only occasionally does Goiffon refer to the literature, and therefore he gives only a short bibliography. The tables, illustrations and figures are good but too few. This manual is an excellent source of information on a subject which has been neglected in this country.